BMJ Open

Association between asthma with dry eye disease: A Meta-Analysis based on observational studies.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045275
Article Type:	Original research
Date Submitted by the Author:	11-Oct-2020
Complete List of Authors:	huang, qun; Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Ophthalmology; Chengdu University of TCM zheng, yanlin; Chengdu University of Traditional Chinese Medicine Affiliated Hospital zhang, chuantao; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, wanjie; Chengdu University of Traditional Chinese Medicine Affiliated Hospital liao, tingting; Chengdu University of Traditional Chinese Medicine Affiliated Hospital xiao, xili; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, jing; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, juan; Chengdu University of Traditional Chinese Medicine Affiliated Hospital
Keywords:	Medical ophthalmology < OPHTHALMOLOGY, Asthma < THORACIC MEDICINE, Paediatric ophthalmology < OPHTHALMOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association between asthma with dry eye disease: A Meta-Analysis based on observational studies.

Running title: asthma and DED

Huang Qun[1]*, M.M., Zheng Yanlin [2†], M.M., Zhang Chuantao[3], M.D., Wang Wanjie [1], M.M., Liao Tingting[4], Xiao Xili [1], M.M., Wang Jing [1], M.M., Wang Juan[1], M.B

1 Department of Ophthalmology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

2 Clinical Medical College, Chengdu University of Traditional Chinese Medicine, Chengdu, China.

3 Department of Respiratory Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

4. Department of endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

* first author, E-mail: skirth@163.com

† Corresponding author, E-mail: zyl3327@163.com

Abbreviations: DED, dry eye disease; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; MeSH, Medical Subject Headings; OR, odds ratio; NOS, Newcastle-Ottawa Scale;

Abstract

Backgound

Studies have shown that dry eye disease (DED) is related to asthma, but these views are still controversial.

Objective

The purpose of this study was to systematically review the relationship between DED and asthma based on the published literature of population-based studies.

Methods

Observational studies addressed the association between asthma and DED were searched on three electronic databases (PubMed, EMBASE, and ISI Web of Science) from their inception up to October 1, 2019. Search terms included a combination of Medical Subject Headings (MeSHs) and free words related to “asthma” and “dry eye diseases”. Two reviewers independently conducted the literature search, data extraction and quality assessment, and were blinded to the other reviewer. The associations were indicated as odds ratio (OR) with 95% confidence interval (95% CI) and combined using RevMan 5.3 software. Subgroup analysis according to ethnicity was performed to test the influence of ethnicity on the association.

Results

Six independent studies were included in this review, and have an average of 7 stars by Newcastle-Ottawa Scale (NOS). Our current findings suggested that the prevalence of DED was higher in the asthma group than that in control (Z = 7.42, P<0.00001; OR 1.29, 95%CI 1.20, 1.38). In the subgroup analysis by ethnicity, Australian, Caucasian and Asian with asthma showed the increased risk of DED.

Conclusion

The results of our meta-analysis quantified a clear association between asthma and DED in the overall population. Patients with asthma had an increased chance of developing DED, and this difference in correlation existed among different countries. However, this significant association may not reflect a causal effect due to the cross-sectional design of included studies.

Strengths and limitations of this study

1. To our knowledge, this is the first meta-analytical report to evaluate the association of asthma and DED.

2. Our analysis included an in-depth and extensive literature search that included six studies, presented data of sufficient quality, and calculated outcome measures that were independent of the risk of research bias.

3. The results of our meta-analysis quantified a clear association between asthma and DED.

4. However, our research has some limitations in interpreting the results. As a general defect in the meta-analysis of observational studies, we cannot rule out the possibility that certain residual factors may link asthma and DED, such as environmental factors and the use of asthma medications.

5. Due to geographic and cultural differences, the lack of universal diagnostic criteria can affect the association between asthma and the incidence of DED.

Keywords

Dry eye disease; asthma; meta-analysis.

1. Introduction

DED has been the focus of attention in recent years, as it is one of the main reasons for seeking eye care in an eye clinics [1]. According to surveys, the prevalence of DED is estimated to be between 5% and 50% [2-8], which frequency increases with age [9]. The economic burden and impact of DED is considerable, in terms of vision, quality of life, work productivity, psychological and physical impact of pain, and so forth. Therefore, as a result of the significant decline in work efficiency, indirect costs account for the largest proportion of total costs [8, 10, 11].

Dry eye disease (DED) is considered to be a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles [12]. Clear factors currently known to be associated with the onset of DED include age, gender, and hormones, but in recent years it has also been found that the association of DED with asthma, allergic rhinitis, and atopic dermatitis [13].

Asthma is one of the most common chronic immunological diseases in humans, but is largely undiagnosed and undertreated in China. Approximately 300 million people worldwide are affected by asthma and about 7.5% of adults in the United States are affected [14]. Its mortality rate is estimated to 0.19 deaths per 100 000 people [15, 16]. The etiology of asthma is multifactorial, including atopic sensitization [17], viral respiratory infections [18], environmental exposures [19], obesity [20] and smoke [21]. Asthma is considered to be the result of complex genetic-environmental interaction, with heterogeneity in clinical manifestation and the type and intensity of airway inflammation and remodeling [22].

Increasing evidence suggests that DED is associated with a high risk of ocular allergy [23, 24]. Ocular allergy, particularly the severe forms of keratoconjunctivitis, has an impact on different key mechanisms of the DED, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities [25]. And patients with asthma also often have allergic comorbidities such as allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy, drug allergy [26, 27]. Recently, several studies have highlighted the possible relationship between dry eye disease and asthma [28, 29]. However, a possible relationship between asthma and DED is still under investigation and the well-established information is very limited. To the best of our knowledge, no published meta-analysis has been performed to assess the relationship between asthma and DED. Thus, we performed the current meta-analysis to determine whether there is a link between asthma and DED and to use a meta-analytic approach to quantify such associations.

2. Methods

This systematic review and meta-analysis conformed to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [30]. Ethical approval, informed consent, Patient and public involvement statement were not necessary, because all the data used for analyses were extracted from available publications. The Meta-Analysis has been registered in the Open Science Framework(OSF) (registration number: DOI 10.17605/OSF.IO/UHN38).

2.1. Literature search strategy

Referring to the search strategy suggested by Cochrane, two researchers independently and systematically searched three electronic databases, including PubMed, EMBASE, and ISI Web of Science, from the database inception date until October 1, 2019 without language restrictions. A combination of Medical Subject Terms (MeSHs) and free terms was used to retrieve possibly eligible publications in each electronic database, and the English search strategy was as follows: (asthma or wheeze or “Asthma”[MeSH]) and (dry eye or dry eye disease or Keratoconjunctivitis Sicca or Xerophthalmia or Sjogren's Syndrome or “Dry eye syndrome”[MeSH]). For Chinese academic databanks, we used “gan yan” and “xiao chuan” to identify relevant Chinese articles. We also manually screened the reference lists of original and review articles for additionally eligible studies.

2.2. Inclusion Criteria

The inclusion criteria were as follow: (i) the diagnosis of asthma and DED in the study group was based on well-established criteria or according to a clinical diagnosis made by clinical physicians; (ii) control subjects should be free of any history of asthma or DED, no specific restriction on gender and age was imposed; (iii) types of study were observational studies including cross-sectional studies, cohort studies, case-control studies or epidemiological studies; (iv) the main outcome was the association between DED and asthma, as indicated by OR and the associated 95%CI, which should be either provided directly in the original article or could be calculated based on the original data. If studies with overlapping participants were encountered, the reports with the largest sample and the most recent reports were included in the present meta-analysis. If no data is available in the original article, the corresponding author of relevant study would be contacted via email. If the corresponding author did not response after we sent three e-mails, this article would not be used for quantitative synthesis. Abstracts, editorial letters, reviews, case reports, book chapters and organizational guidelines were excluded from the present analysis.

Data extraction

According to the predetermined inclusion criteria, two reviewers (XXL and WJ) independently conducted the literature search, data extraction and quality assessment, and were blinded to the findings of the other reviewer. After a rigorous screening, the

following data regarding the characteristics of the studies were extracted using a standardized collection form: first author, year of publication, country where the study was conducted, sample size, demographic characteristics of participants in different groups, strategies for confirmation of DED and asthma, adjustment of confounding factors for effect assessment. Disagreements occurred during the study selection was resolved through discussion with a third reviewer (ZYL) until a mutual consensus was reached.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in case-control and cohort studies [31]. The methodological quality of the cross-sectional studies was evaluated following the standards of the Agency for Healthcare Research and Quality (AHRQ) [32]. Two reviewers（WWJ and WJ）independently conducted quality assessment of included studies and compared the results afterwards. The third reviewer (ZYL) was consulted for help in case of discrepancies regarding the quality assessment.

Data Synthesis and Analysis

RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for the meta-analysis and subgroup analysis. The association between asthma and DED was estimated using adjusted OR and unadjusted OR, the upper and lower limits of the 95%CI were extracted from each study. The confounding factors considered included age and gender. Before combing date from the included studies, statistical heterogeneity among studies for each outcome was estimated using a standard Chi-square test and the Higgins I^2 test ($P>0.1$ and $I^2<50\%$ indicated acceptable heterogeneity [33]). In meta-analyses of multiple studies for a specific outcome, a random-effect estimate was calculated for pooling data across studies if statistical heterogeneity existed; however, if a low heterogeneity was detected in the meta-analysis, a random-effect estimate was also calculated, as the validity of tests of heterogeneity could be limited with a small number of component studies. In case of high heterogeneity, subgroup analysis was carried out by ethnicity, as it was the only confounding factor consistently presented in our selected studies. Sensitivity analysis was conducted by omitting one study at a time and evaluating the resulting effect to determine the potential source of heterogeneity. Begg's rank correlation test and Egger's linear regression test via Stata version 12.0 (Stata Corp LP, USA) were employed to evaluate publication bias. $P < 0.05$ (1-sided) was considered statistically significant, except for tests of heterogeneity.

Results

Literature search results

A total of 231 potential literature citations were searched initially, including 71 records from PubMed, 78 from EMBASE, and 82 from ISI Web of Science (Fig 1). And 27 duplicate articles were excluded. Based on the predetermined selection criteria, 198 studies were excluded at the title and abstract stages, and 6 potentially relevant studies were selected and retrieved for a full-text reading and evaluation of data integrity. Finally, a total of 6 studies [13, 28, 29, 34-36] met all the inclusion criteria for this systematic review and were included.

Study characteristics

Overall, the sample sizes of the included literature ranged from 1174 to 105794, of which a total of 45215 patients with asthma and 232864 control subjects were included. The included studies were published between 2003 and 2018 and involved different ethnicities, including Arabian, Australian, Asian, and Caucasian. Assessment of asthma and DED were inconsistent between studies, and detailed data on main characteristics of these studies were shown in Table 1.

Risk of bias assessment

The methodological quality of included studies was considered low to high according to the NOS. Six included studies achieved an average of 7 stars, and two studies [28, 34] gained nine stars (Table 2).

Table 1. Main characteristics of included studies

Study	Country	Ethnicity	Sample size	Mean age	Definition of asthma	Definition of DED	Adjustment for confounders
Abdulaziz, 2017	Saudi Arabia	Arabian	Asthma: 139 Control: 1719	39.3	Questionnaire	Six-item questionnaire	Age, gender and smoking
Chia, 2003	Australia	Australian	Asthma: 135 Control: 1039	60.8	Medical history of confirmed diagnosis	Interviewer-administered questionnaire	Age and gender
Huang, 2018	Taiwan	Asian	Asthma: 41229 Control: 164916	49.56	ICD-9-CM 493	ICD-9-CM 375.15	Age and gender
Kim, 2016	Korea	Asian	Asthma: 556 Control: 16494	50.88	Medical history	Interviewer-administered questionnaire	Age, gender, residential area, education level, occupation and history of eye surgery
Vehof, 2014	UK	Caucasian	Asthma: 608 Control: 3216	57.1	Medical history	ICD-9-CM 375.15	Age and gender
Wang, 2012	Taiwan	Asian	Asthma: 2548 Control: 45480	52.4	Elixhauser comorbidity index	ICD-9-CM 375.15	Age, gender, urbanization levels and monthly incomes

DED: dry eye disease.

Table 2. Quality assessment of included studies according to the Newcastle-Ottawa scale.

Item/Study	Abdulaziz, 2017	Chia, 2003	Huang, 2018	Kim, 2016	Vehof, 2014	Wang, 2012
Adequate definition of cases	*	*	*	*	*	*
Representativeness of cases	*	-	*	*	-	*
Selection of control subjects	-	-	*	*	-	*
Definition of control subjects	*	*	*	*	*	*
Control for important factor or additional factor	-	-	**	-	*	**
Exposure assessment	*	*	*	*	*	*
Same method of ascertainment for all subjects	*	*	*	*	*	*
Non-response rate	*	*	*	*	*	*

A study could be awarded a maximum of one star for each item except for the item “Control for important factor or additional factor”.
The definition/explanation of each column of the Newcastle-Ottawa Scale is available from (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Meta-analyses Results

A random effect model was selected to analyze the effect size with modest heterogeneity among the studies (I^2 = 23%, P =0.26). The asthma group had significantly higher prevalence of DED compared to control group (OR 1.29, 95%CI 1.20, 1.38; P<0.00001). In other words, there was a significant association between the presence of asthma and DED (Fig 2). Owing to a lack of data, it was not possible to detect the association between asthma and diverse subtypes of DED.

Subgroup analysis and sensitivity analysis

Subgroup-analysis was performed according to ethnicity (Fig 3). In the stratified analysis by ethnicity, a statistically significant correlation was detected in Australian (OR 1.60, 95%CI 1.00, 2.56; P=0.05), Caucasian (OR 1.54, 95%CI 1.17, 2.03; P=0.002), Asian (OR 1.29, 95%CI 1.23, 1.35; P<0.00001) countries, but this association was not significant among Arabian population (OR 0.96, 95%CI 0.63, 1.46; P=0.85).

Sensitivity analysis and publication bias

The funnel plot for the association between asthma and DED was symmetrical in vision (Fig 4), the Begg's test (z=0.38, P=0.727) and Egger's test (t=-0.40, P=0.708) also suggested no statistically significant publication bias. Sensitivity analysis confirmed the robustness of our conclusion (detailed data not shown).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the association between asthma and DED, which examines a large dataset of 6 studies with a total of 278079 participants. Our current findings suggested that asthma patients had a higher risk of developing DED than the non-asthma subjects, and this significant correlation could be observed in different ethnicities expect for Arabians. In the subgroup analysis of study location, Australian, Caucasian and Asian patients with asthma showed increased risk of DED.

There have been some population-based studies that have emphasized the possible relationship between DED and asthma. Chia et al. [29] found that after adjusting for age and gender factors, asthma is a systemic factor closely related to DED. Dogru et al. [37] found that the mean measurement of tear film breakup time was significantly lower in asthma than control, and the presence of tear film instability was higher in children with asthma, which may lead to DED in the future. Furthermore, in terms of treatment, Huang et al. [28] found that patients taking asthma-related treatments including leukotriene receptor antagonists, antihistamines, and inhaled corticosteroids were at greater risk for DED. Bielory [38] found that antihistaminic and anti-inflammatory agents used in the treatment of asthma and allergy, may exacerbate

dry-eye complaints that commonly complicate symptoms with various forms of tear film dysfunction or conjunctival hyperreactivity.

Asthma is a consequence of complex gene-environment interactions, and is an inflammatory response triggered by exposure to allergens, infection, or irritants[22, 39]. Innate and adaptive cells, including eosinophils, mast cells, lymphocytes, neutrophils, and monocytes, are activated to express or derive cytokines and chemokines and enhance inflammation and airway hyperresponsiveness, leading to airway remodeling [40]. By contrast, the most widely accepted hypothesis for the pathogenesis of dry eye disease is immunological mechanism [41] and inflammation [42, 43]. There is potential for the ocular homeostasis to be altered by innate and adaptive cells such as neutrophils, lymphocytes, eosinophils, NK cells, macrophages, and result in inflammatory processes that compromise both the tear film and ocular surface integrity [44]. Although the exact mechanism of DED and asthma is not completely clear, the pathogenesis of both diseases is closely related to inflammation, which may have some shared biological pathways.

Asthma and DED are common clinical diseases, and there is still no evidence to support a causal relationship between asthma and DED, which may have a common pathophysiological mechanism even if they occur independently. Clinicians need to diagnose the possibility of both asthma and dry eye syndrome. Asthma patients should strengthen prevention and treatment of DED, and try to avoid the risk factors of DED and iatrogenic DED, including wearing contact lens, long-term use of visual display terminal, refractive or cataract surgery [45, 46].

Limitations

Our analysis included an in-depth and extensive literature search that included six studies, presented data of sufficient quality, and calculated outcome measures that were independent of the risk of research bias. However, our research has some limitations in interpreting the results. As a general defect in the meta-analysis of observational studies, first, we cannot rule out the possibility that certain residual factors may link asthma and DED, such as environmental factors and the use of asthma medications. Second, due to geographic and cultural differences, the lack of universal diagnostic criteria can affect the association between asthma and the incidence of DED. Finally, the results of this study do not indicate a causal relationship between asthma and DED. We recognize that this is a limitation, thus the results should be interpreted cautiously.

Conclusions

The results of our meta-analysis show that asthma patients have a higher risk of developing DED than the subjects without asthma, and this relationship is significant in Australians, Caucasians, and Asians. However, this association may not reflect cause and effect if unidentified confounders account for the results. These data

suggest that patients with asthma may be at risk of carrying a comorbid diagnosis of DED, and should try to avoid risk factors and strengthen the prevention of DED.

Author contribution

Huang Qun and Zheng yanlin planned and designed the study. Xiao Xili and Wang Jing conducted rigorous literature searches and data extraction. Wang Wanjie, Liao Tingting and Wang Juan conducted the data preparation, quality assessments, and data analyses. Huang Qun and Zhang Chuantao wrote and revised the manuscript. All the authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there are no competing interests associated with the manuscript.

Funding

This work was supported by Sichuan Science and technology program(grant number 2020JDRC0114), "Xinglin scholar" Research Premotion Project of Chengdu University of Traditional Chinese Medicine(grant number XSGG2019016、XGZX2003、JSZX005), "100 Talent Plan" Project of Hospital of Chengdu University of Traditional Chinese Medicine (grant number Hospital office [2020] 42), National training program for innovative backbone talents of traditional Chinese Medicine (grant number No. 91 [2019] of the State Office of Traditional Chinese Medicine), Science and technology development fund of Hospital of Chengdu University of traditional Chinese Medicine （grant number 19LW19、18MZ12）. The funder has provided only financial support for the study.

References

1. Bradley, J.L., et al., *Dry eye disease ranking among common reasons for seeking eye care in a large US claims database.* Clin Ophthalmol, 2019. **13**: p. 225-232.

2. Dana, R., et al., *Estimated Prevalence and Incidence of Dry Eye Disease Based on Coding Analysis of a Large, All-age United States Health Care System.* Am J Ophthalmol, 2019. **202**: p. 47-54.

3. Yasir, Z.H., et al., *Prevalence and Determinants of Dry Eye Disease among 40 Years and Older Population of Riyadh (Except Capital), Saudi Arabia.* Middle East Afr J

Ophthalmol, 2019. **26**(1): p. 27-32.

4. Tan, L.L., et al., *Prevalence of and risk factors for symptomatic dry eye disease in Singapore.* Clin Exp Optom, 2015. **98**(1): p. 45-53.

5. Song, P., et al., *Variations of dry eye disease prevalence by age, sex and geographic characteristics in China: a systematic review and meta-analysis.* J Glob Health, 2018. **8**(2): p. 020503.

6. Caffery, B., et al., *Prevalence of dry eye disease in Ontario, Canada: A population-based survey.* Ocul Surf, 2019. **17**(3): p. 526-531.

7. Titiyal, J.S., et al., *Prevalence and risk factors of dry eye disease in North India: Ocular surface disease index-based cross-sectional hospital study.* Indian J Ophthalmol, 2018. **66**(2): p. 207-211.

8. Stapleton, F., et al., *TFOS DEWS II Epidemiology Report.* Ocul Surf, 2017. **15**(3): p. 334-365.

9. Rapoport, Y., et al., *A Comprehensive Review of Sex Disparities in Symptoms, Pathophysiology, and Epidemiology of Dry Eye Syndrome.* Semin Ophthalmol, 2016. **31**(4): p. 325-36.

10. Uchino, M., *What We Know About the Epidemiology of Dry Eye Disease in Japan.* Invest Ophthalmol Vis Sci, 2018. **59**(14): p. 17-23491.

11. McDonald, M., et al., *Economic and Humanistic Burden of Dry Eye Disease in Europe, North America, and Asia: A Systematic Literature Review.* Ocul Surf, 2016. **14**(2): p. 144-67.

12. Craig, J.P., et al., *TFOS DEWS II Definition and Classification Report.* Ocul Surf, 2017.

15(3): p. 276-283.

13. Kim, M., et al., *Dry eye disease and allergic conditions: A Korean nationwide population-based study.* Am J Rhinol Allergy, 2016. **30**(6): p. 397-401.

14. Nanda, A. and A.N. Wasan, *Asthma in Adults.* Med Clin North Am, 2020. **104**(1): p. 95-108.

15. Ebmeier, S., et al., *Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012).* Lancet, 2017. **390**(10098): p. 935-945.

16. Huang, K., et al., *Prevalence, risk factors, and management of asthma in China: a national cross-sectional study.* Lancet, 2019. **394**(10196): p. 407-418.

17. Holt, P.G. and P.D. Sly, *Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment.* Nat Med, 2012. **18**(5): p. 726-35.

18. Busse, W.W., R.F. Lemanske, Jr., and J.E. Gern, *Role of viral respiratory infections in asthma and asthma exacerbations.* Lancet, 2010. **376**(9743): p. 826-34.

19. Sbihi, H., et al., *Thinking bigger: How early-life environmental exposures shape the gut microbiome and influence the development of asthma and allergic disease.* Allergy, 2019. **9**(10): p. 13812.

20. Leiria, L.O., M.A. Martins, and M.J. Saad, *Obesity and asthma: beyond T(H)2 inflammation.* Metabolism, 2015. **64**(2): p. 172-81.

21. Hedman, L., et al., *Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers.* Thorax, 2011. **66**(1): p. 20-5.

22. Papi, A., et al., *Asthma.* Lancet, 2018. **391**(10122): p. 783-800.

23. Enriquez-de-Salamanca, A., S. Bonini, and M. Calonge, *Molecular and cellular biomarkers in dry eye disease and ocular allergy.* Curr Opin Allergy Clin Immunol, 2012. **12**(5): p. 523-33.

24. Chen, L., et al., *High incidence of dry eye in young children with allergic conjunctivitis in Southwest China.* Acta Ophthalmol, 2016. **94**(8): p. e727-e730.

25. Villani, E., G. Rabbiolo, and P. Nucci, *Ocular allergy as a risk factor for dry eye in adults and children.* Curr Opin Allergy Clin Immunol, 2018. **18**(5): p. 398-403.

26. Heck, S., et al., *High probability of comorbidities in bronchial asthma in Germany.* NPJ Prim Care Respir Med, 2017. **27**(1): p. 017-0026.

27. Masuda, S., et al., *High prevalence and young onset of allergic rhinitis in children with bronchial asthma.* Pediatr Allergy Immunol, 2008. **19**(6): p. 517-22.

28. Huang, Y.C., et al., *Association between dry eye disease and asthma: a nationwide population-based study.* PeerJ, 2018. **5**(6).

29. Chia, E.M., et al., *Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study.* Clin Exp Ophthalmol, 2003. **31**(3): p. 229-32.

30. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS Med, 2009. **6**(7): p. 21.

31. GA Wells, B.S., D O'Connell, J Peterson, V Welch, M Losos, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

32. Program, T.A. *Agency for Healthcare Research and Quality*. Available from: http://www.ahrq.gov/research/findings/ta/index.html.

33. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* Bmj, 2003. **327**(7414): p. 557-60.

34. Wang, T.J., et al., *Comorbidities of dry eye disease: a nationwide population-based study.* Acta Ophthalmol, 2012. **90**(7): p. 663-8.

35. Vehof, J., et al., *Prevalence and risk factors of dry eye disease in a British female cohort.* Br J Ophthalmol, 2014. **98**(12): p. 1712-7.

36. Alshamrani, A.A., et al., *Prevalence and Risk Factors of Dry Eye Symptoms in a Saudi Arabian Population.* Middle East Afr J Ophthalmol, 2017. **24**(2): p. 67-73.

37. Dogru, M., et al., *Evaluation of the tear film instability in children with allergic diseases.* Cutan Ocul Toxicol, 2016. **35**(1): p. 49-52.

38. Bielory, L., *Ocular toxicity of systemic asthma and allergy treatments.* Curr Allergy Asthma Rep, 2006. **6**(4): p. 299-305.

39. Gibson, P.G. and V.M. McDonald, *Management of severe asthma: targeting the airways, comorbidities and risk factors.* Intern Med J, 2017. **47**(6): p. 623-631.

40. Guida, G. and A.M. Riccio, *Immune induction of airway remodeling.* Semin Immunol, 2019. **14**(101346): p. 101346.

41. Barabino, S., et al., *Ocular surface immunity: homeostatic mechanisms and their disruption in dry eye disease.* Prog Retin Eye Res, 2012. **31**(3): p. 271-85.

42. Wei, Y. and P.A. Asbell, *The core mechanism of dry eye disease is inflammation.* Eye Contact Lens, 2014. **40**(4): p. 248-56.

43. Yamaguchi, T., *Inflammatory Response in Dry Eye.* Invest Ophthalmol Vis Sci, 2018. **59**(14): p. 17-23651.

44. Reyes, J.L., et al., *Innate and Adaptive Cell Populations Driving Inflammation in Dry Eye Disease.* Mediators Inflamm, 2018. **12**(2532314).

45. Uchino, M., et al., *Prevalence and risk factors of dry eye disease in Japan: Koumi study.* Ophthalmology, 2011. **118**(12): p. 2361-7.

46. Gomes, J.A.P., et al., *TFOS DEWS II iatrogenic report.* Ocul Surf, 2017. **15**(3): p. 511-538.

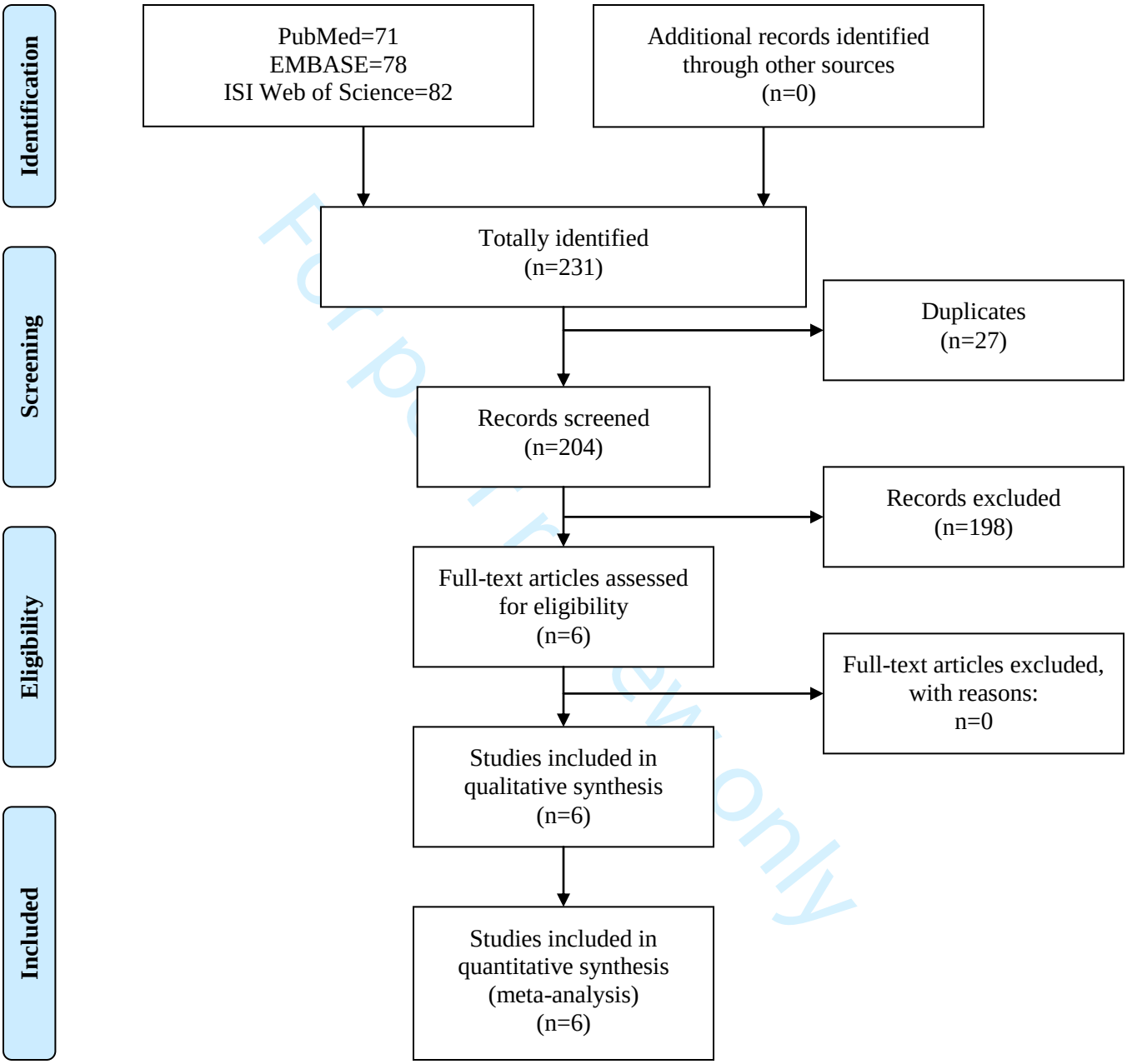
Figure Legends

Figure 1. Flow chart of literature search.

Figure 2. Meta-analysis of asthma and DED using a random-effects model.

Figure 3. Subgroup analysis by ethnicity of asthma and DED.

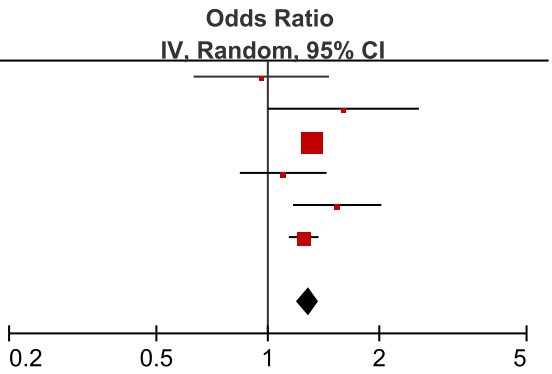
Figure 4. Funnel plot of a meta-analysis of asthma and DED.

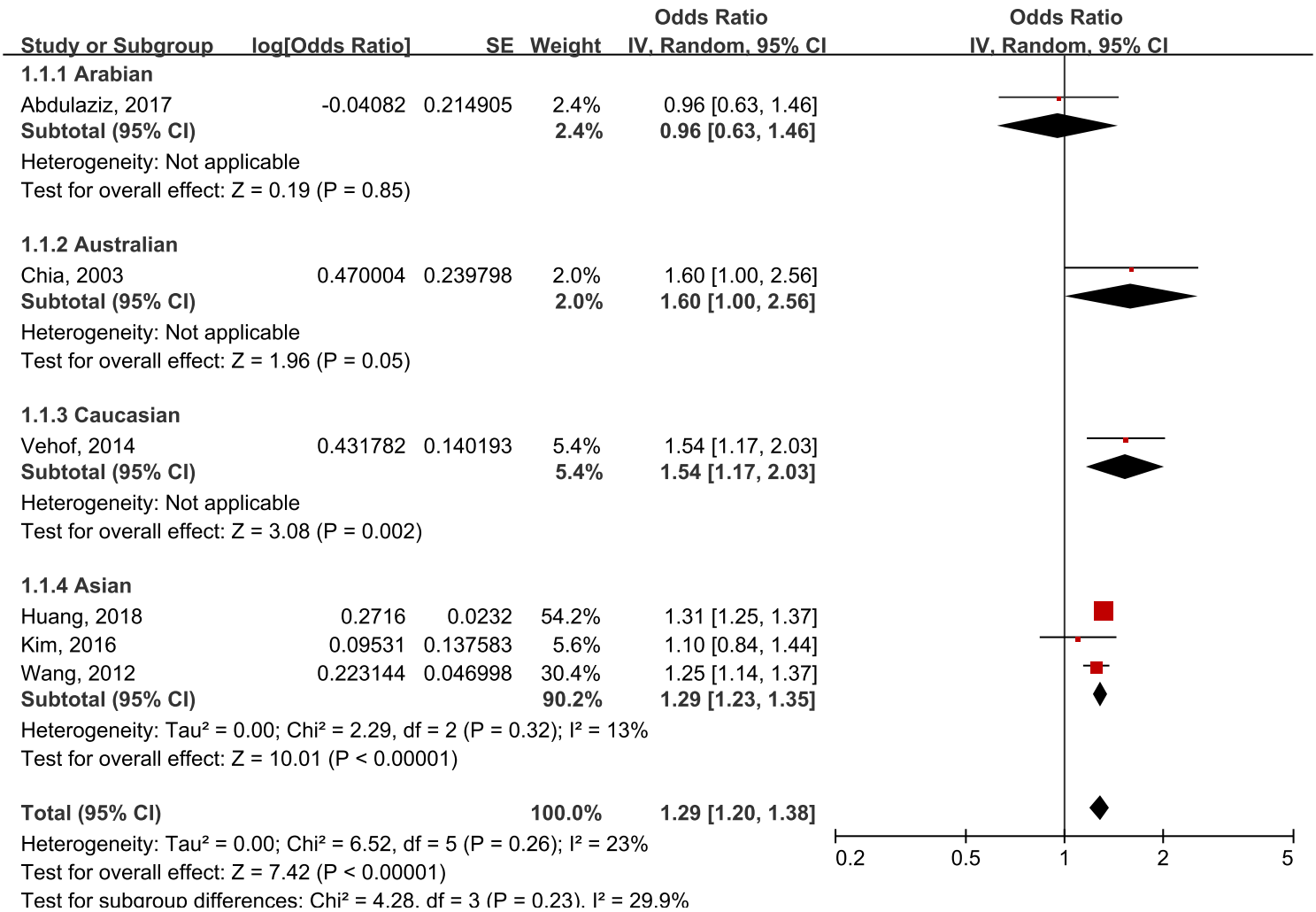


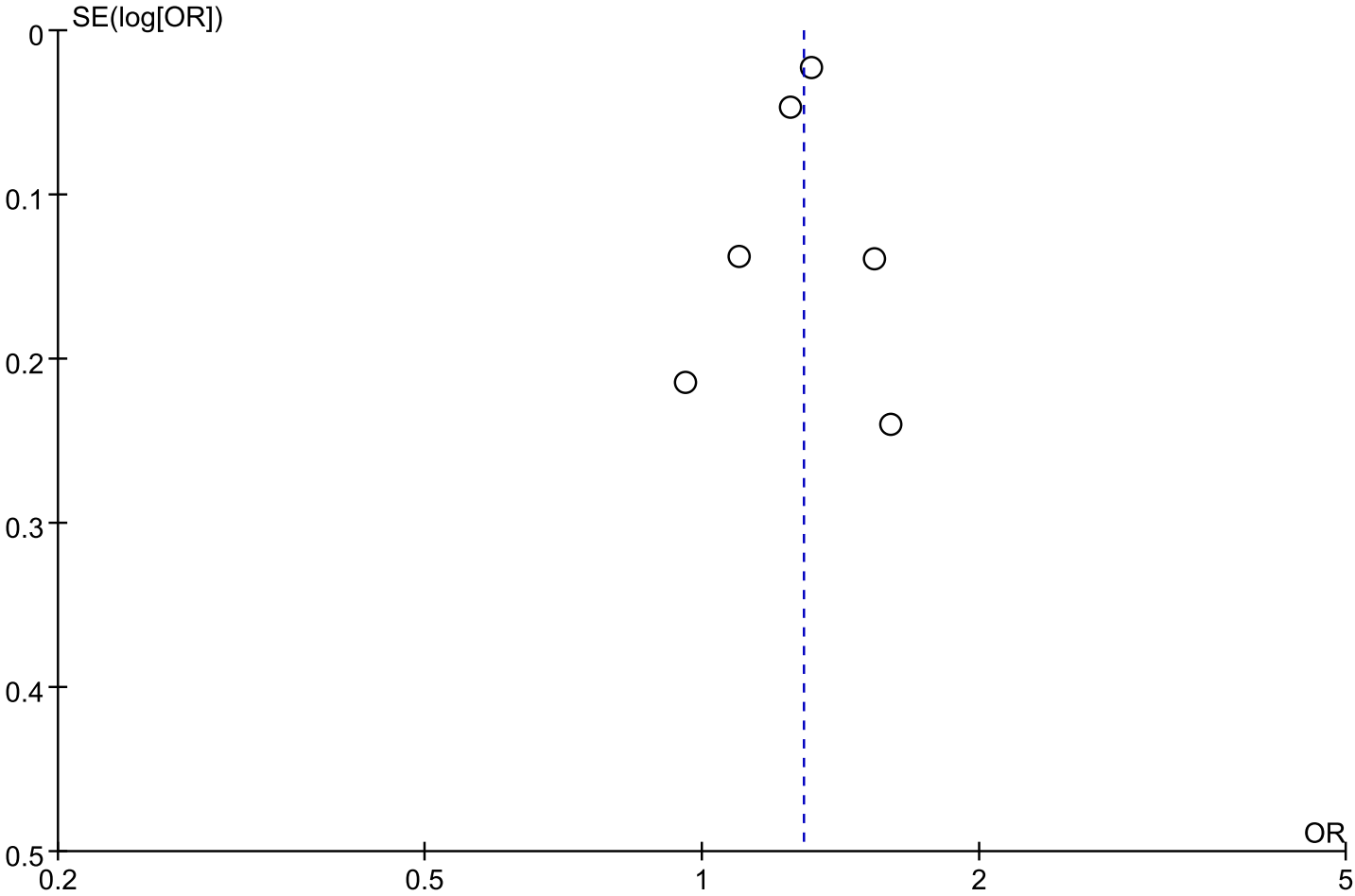
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Abdulaziz, 2017	-0.04082	0.214905	2.4%	0.96 [0.63, 1.46]
Chia, 2003	0.470004	0.239798	2.0%	1.60 [1.00, 2.56]
Huang, 2018	0.2716	0.0232	54.2%	1.31 [1.25, 1.37]
Kim, 2016	0.09531	0.137583	5.6%	1.10 [0.84, 1.44]
Vehof, 2014	0.431782	0.140193	5.4%	1.54 [1.17, 2.03]
Wang, 2012	0.223144	0.046998	30.4%	1.25 [1.14, 1.37]
Total (95% CI)			**100.0%**	**1.29 [1.20, 1.38]**

Heterogeneity: Tau² = 0.00; Chi² = 6.52, df = 5 (P = 0.26); I² = 23%

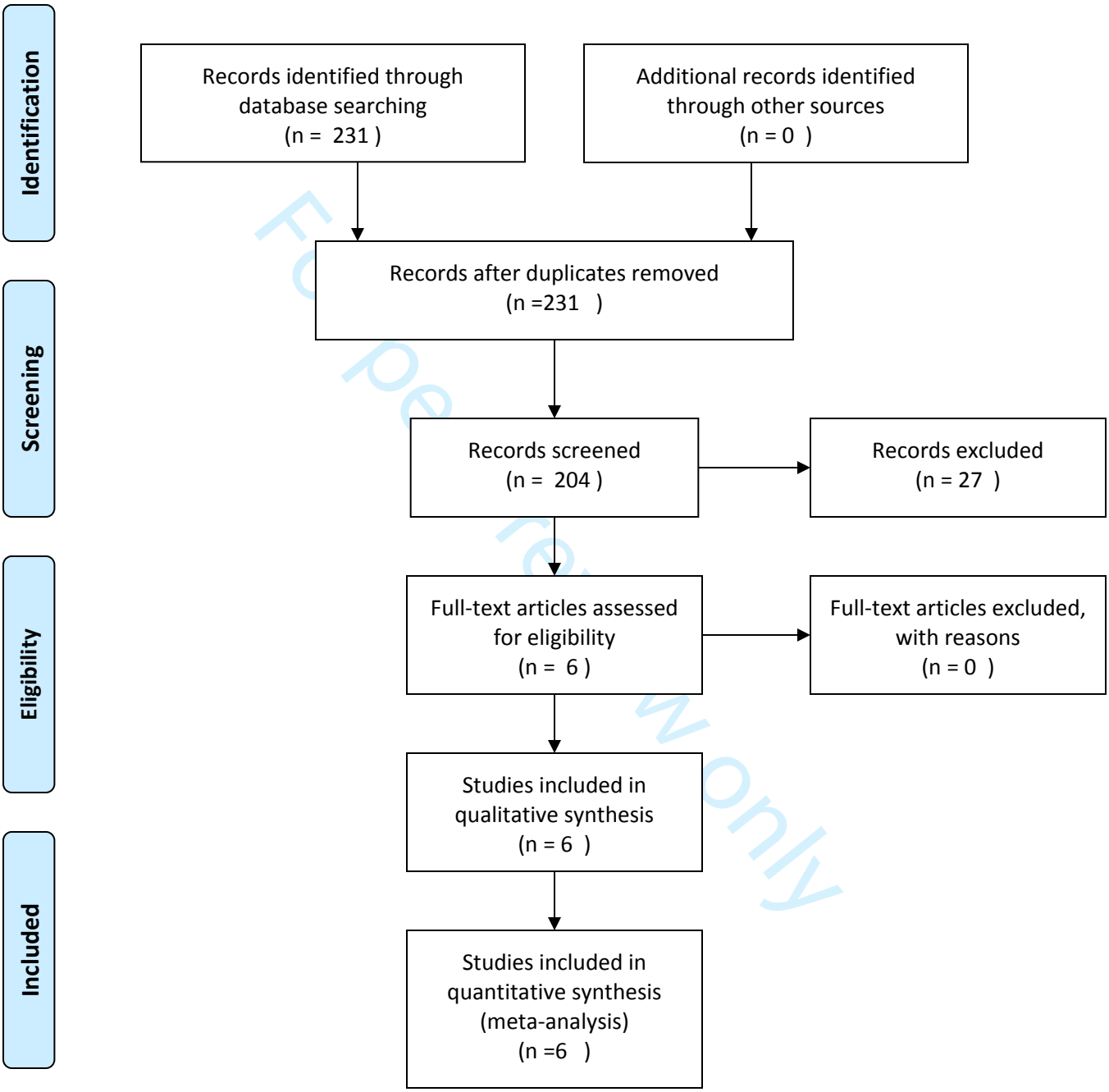
Test for overall effect: Z = 7.42 (P < 0.00001)




Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Arabian
Abdulaziz, 2017 -0.04082 0.214905 2.4% 0.96 [0.63, 1.46]
Subtotal (95% CI) 2.4% 0.96 [0.63, 1.46]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
1.1.2 Australian
Chia, 2003 0.470004 0.239798 2.0% 1.60 [1.00, 2.56]
Subtotal (95% CI) 2.0% 1.60 [1.00, 2.56]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)
1.1.3 Caucasian
Vehof, 2014 0.431782 0.140193 5.4% 1.54 [1.17, 2.03]
Subtotal (95% CI) 5.4% 1.54 [1.17, 2.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.08 (P = 0.002)
1.1.4 Asian
Huang, 2018 0.2716 0.0232 54.2% 1.31 [1.25, 1.37]
Kim, 2016 0.09531 0.137583 5.6% 1.10 [0.84, 1.44]
Wang, 2012 0.223144 0.046998 30.4% 1.25 [1.14, 1.37]
Subtotal (95% CI) 90.2% 1.29 [1.23, 1.35]
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 10.01 (P < 0.00001)
Total (95% CI) 100.0% 1.29 [1.20, 1.38]
Heterogeneity: Tau² = 0.00; Chi² = 6.52, df = 5 (P = 0.26); I² = 23%
Test for overall effect: Z = 7.42 (P < 0.00001)
Test for subgroup differences: Chi² = 4.28, df = 3 (P = 0.23), I² = 29.9%
0.2
0.5
1
2
5


SE(log[OR])
0
0.1
0.2
0.3
0.4
0.5
0.2
0.5
1
2
5
OR

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Association between asthma and dry eye disease: A meta-analysis based on observational studies

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045275.R1
Article Type:	Original research
Date Submitted by the Author:	20-May-2021
Complete List of Authors:	huang, qun; Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Ophthalmology; Chengdu University of TCM Zheng, Yanlin; Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Ophthalmology; Chengdu University of Traditional Chinese Medicine, zhang, chuantao; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, wanjie; Chengdu University of Traditional Chinese Medicine Affiliated Hospital liao, tingting; Chengdu University of Traditional Chinese Medicine Affiliated Hospital xiao, xili; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, jing; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, juan; Chengdu University of Traditional Chinese Medicine Affiliated Hospital
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Ophthalmology
Keywords:	Medical ophthalmology < OPHTHALMOLOGY, Asthma < THORACIC MEDICINE, Paediatric ophthalmology < OPHTHALMOLOGY, Orbital and lacrimal disorders < OPHTHALMOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association between asthma and dry eye disease: A meta-analysis based on observational studies

Running title: asthma and DED

Huang Qun[1]*, M.M., Zheng Yanlin [2†], M.M., Zhang Chuantao[3], M.D., Wang Wanjie [1], M.M., Liao Tingting[4], Xiao Xili [1], M.M., Wang Jing [1], M.M., Wang Juan[1], M.B

1 Department of Ophthalmology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

2 Clinical Medical College, Chengdu University of Traditional Chinese Medicine, Chengdu, China.

3 Department of Respiratory Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

4. Department of endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

* first author, E-mail: skirth@163.com

† Corresponding author, E-mail: zhengyanlin@cdutcm.edu.cn

Abbreviations: DED, dry eye disease; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; MeSH, Medical Subject Headings; OR, odds ratio; NOS, Newcastle-Ottawa Scale;

ABSTRACT

Objective

This study aimed to systematically review the relationship between DED and asthma based on published population-based studies.

Design

Systematic review and meta- analysis.

Methods and analysis

Observational studies addressing the association between asthma and DED were searched using three electronic databases (PubMed, EMBASE, and ISI Web of Science) from their inception up to October 1, 2019. Search terms included a combination of Medical Subject Headings and free words related to “asthma” and “dry eye disease.” Two reviewers independently conducted the literature search, data extraction, and quality assessment and were blinded to the other reviewers. The associations were indicated as odds ratios (ORs) with 95% confidence intervals (95% CIs) and combined using RevMan 5.3 software. Subgroup analysis according to ethnicity was performed to test the influence of ethnicity on the association.

Results

Six independent studies were included in this review and had an average of seven stars by the Newcastle-Ottawa Scale. Our current findings suggest that the prevalence of DED was higher in the asthma group than in the control group ($Z = 7.42$, $P<0.00001$; OR 1.29, 95% CI 1.20–1.38). In the subgroup analysis by ethnicity, Australian, Caucasian, and Asian patients with asthma showed an increased risk of DED.

Conclusion

The results of our meta-analysis showed a clear association between asthma and DED in the overall population. Patients with asthma had an increased chance of developing DED, and this difference in the correlation existed among different countries. However, this significant association may not reflect a causal effect due to the cross-sectional design of the included studies.

OSFregistration number DOI 10.17605/OSF.IO/UHN38).

Strengths and limitations of this study

1. This is the first meta-analytical report to evaluate the association between asthma and DED.
2. The results of our meta-analysis revealed a clear association between asthma and DED.

3. As a general defect in the meta-analysis of observational studies, we cannot rule out the possibility that certain residual factors that may link asthma and DED.

4. Due to geographic and cultural differences, the lack of universal diagnostic criteria can affect the association between asthma and the incidence of DED.

Keywords

Dry eye disease; asthma; meta-analysis

INTRODUCTION

Dry eye disease (DED) has been the focus of attention in recent years, as it is one of the main reasons for seeking eye care in eye clinics.[1] According to surveys, the prevalence of DED is estimated to be between 5% and 50%,[2-8] the frequency of which increases with age.[9] The prevalence is driven mainly by the classification of DED, with the prevalence of signs being much higher (up to 75%) compared to symptoms.[8] The economic burden and impact of DED is considerable in terms of vision, quality of life, work productivity, and the psychological and physical impact of pain. Therefore, indirect costs account for the largest proportion of total costs because of the significant decline in work efficiency.[8, 10, 11]

DED is considered to be a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[12] Clear factors currently known to be associated with the onset of DED include age, sex, and hormones, but in recent years, it has also been found that DED is associated with asthma, allergic rhinitis, and atopic dermatitis.[13]

Asthma is one of the most common chronic immunological diseases in humans, affecting 1%–18% of the population in different countries.[14] Specifically, the prevalence of asthma varies depending on whether the disease is diagnosed by a medical doctor (4.3%), clinical/treated asthma (4.5%), or symptoms such as wheezing (8.6%), and varies by up to 21 times in different countries.[15] Its mortality rate is estimated to 0.19 deaths per 100, 000 people.[16-–17] The etiology of asthma is multifactorial, including atopic sensitization,[18] viral respiratory infections,[19] environmental exposures,[20] obesity,[21] and smoking [22]. Asthma is considered to be the result of complex genetic-environmental interactions, with heterogeneity in the clinical manifestations and the type and intensity of airway inflammation and remodeling.[23]

Increasing evidence suggests that DED is associated with a high risk of ocular allergy. [24-25] Ocular allergy, particularly the severe forms of keratoconjunctivitis, has an impact on different key mechanisms of DED, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities.[26] Moreover, patients with asthma also often have allergic comorbidities such as allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy, and drug allergy.[27-28] Recently, several studies have highlighted the possible relationship between DED and asthma.[29-30] However, a possible relationship between asthma and DED remains under investigation, and well-established information is very limited. To the best of our knowledge, no meta-analysis has been performed to assess the relationship between asthma and DED. Thus, we performed the current meta-analysis to determine whether there is a link between asthma and DED using a meta-analytic approach to quantify such associations.

METHODS

This systematic review and meta-analysis conformed to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[31]

ETHICAL APPROVAL

Ethical approval, informed consent, and patient and public involvement statements were not necessary because all the data used for the analyses were extracted from available publications. The meta-analysis has been registered in the Open Science Framework (registration number: DOI 10.17605/OSF.IO/UHN38).

LITERATURE SEARCH STRATEGY

Referring to the search strategy suggested by Cochrane, two researchers independently and systematically searched three electronic databases, including PubMed, EMBASE, and ISI Web of Science, from the database inception date until October 1, 2019, without language restrictions. A combination of Medical Subject Terms (MeSHs) and free terms was used to retrieve possibly eligible publications in each electronic database, and the English search strategy was as follows: (asthma or wheeze or "Asthma"[MeSH]) and (dry eye or dry eye disease or keratoconjunctivitis sicca or xerophthalmia or Sjogren's syndrome or "dry eye syndrome" [MeSH]). For Chinese academic databanks, we used "gan yan" and "xiao chuan" to identify relevant Chinese articles. We also manually screened the reference lists of the original and review articles for additional eligible studies.

INCLUSION CRITERIA

The inclusion criteria were as follows: (i) the diagnosis of asthma and DED in the study group was based on well-established criteria or according to a clinical diagnosis made by clinical physicians; (ii) control subjects should be free of any history of asthma or DED, no specific restriction on sex and age was imposed; (iii) types of study were observational studies, including cross-sectional, cohort, case-control, or epidemiological studies; (iv) the main outcome was the association between DED and asthma, as indicated by odds ratio (OR) and the associated 95% confidence intervals (CI), which should be either provided directly in the original article or could be calculated based on the original data. If studies with overlapping participants were encountered, reports with the largest sample and the most recent reports were included in the present meta-analysis. If no data was available in the original article, the corresponding author of the relevant study was contacted via email. If the corresponding author did not respond after we sent three e-mails, this article was not used for quantitative synthesis. Abstracts, editorial letters, reviews, case reports, book chapters, and organizational guidelines were excluded from the analysis.

DATA EXTRACTION

According to the predetermined inclusion criteria, two reviewers (XXL and WJ) independently conducted the literature search, data extraction, and quality assessment and were blinded to the findings of the other reviewer. After rigorous screening, the following data regarding the characteristics of the studies were extracted using a standardized collection form: first author, year of publication, country where the study was conducted, sample size, demographic characteristics of participants in different groups, strategies for confirmation of DED and asthma, and adjustment of confounding factors for effect assessment. Disagreements that occurred during the study selection were resolved through a discussion with a third reviewer (ZYL) until a consensus was reached.

QUALITY ASSESSMENT

The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in case-control and cohort studies.[32] The methodological quality of the cross-sectional studies was evaluated according to the standards of the Agency for Healthcare Research and Quality.[33] Two reviewers (WWJ and WJ) independently conducted quality assessments of the included studies and compared the results. The third reviewer (ZYL) was consulted in case of discrepancies regarding quality assessment.

DATA SYNTHESIS AND ANALYSIS

RevMan 5.3 (Copenhagen: the Nordic Cochrane Center, the Cochrane Collaboration, 2014) was used for the meta-analysis and subgroup analysis. The association between asthma and DED was estimated using adjusted OR and unadjusted OR, and the upper and lower limits of the 95%CI were extracted from each study. The confounding factors included age and sex. Before combining the data from the included studies, statistical heterogeneity among studies for each outcome was estimated using a standard Chi-square test and the Higgins I^2 test ($P>0.1$, $I^2<50\%$ indicated acceptable heterogeneity [34]). In the meta-analyses of multiple studies for a specific outcome, a random-effect estimate was calculated for pooling data across studies if statistical heterogeneity existed; however, if a low heterogeneity was detected in the meta-analysis, a random-effect estimate was also calculated, as the validity of tests of heterogeneity could be limited with a small number of component studies. In the case of high heterogeneity, subgroup analysis was carried out by ethnicity, as it was the only confounding factor consistently presented in our selected studies. Sensitivity analysis was conducted by omitting one study at a time and evaluating the resulting effect to determine the potential source of heterogeneity. Begg's rank correlation test and Egger's linear regression test using Stata version 12.0 (Stata Corp LP, USA) were used to evaluate publication bias. Statistical significance was set at $P < 0.05$ (1-sided), except for tests of heterogeneity.

PATIENT AND PUBLIC INVOLVEMENT

There was no involvement of patients or public during the outline of this project.

RESULTS

LITERATURE SEARCH

A total of 231 potential literature citations were searched initially, including 71 records from PubMed, 78 from EMBASE, and 82 from ISI Web of Science (Figure 1). Additionally, 27 duplicate articles were excluded. Based on the predetermined selection criteria, 198 studies were excluded at the title and abstract stages, and six potentially relevant studies were selected and retrieved for full-text reading and evaluation of data integrity. Finally, six studies [13, 29, 30, 35-37] met all the inclusion criteria for this systematic review and were included.

STUDY CHARACTERISTICS

Overall, the sample sizes of the included studies ranged from 1174 to 105794, of which a total of 45215 patients with asthma and 232864 control subjects were included. The included studies were published between 2003 and 2018 and involved different ethnicities, including Arabian, Australian, Asian, and Caucasian populations. The assessment of asthma and DED was inconsistent between studies, and detailed data on the main characteristics of these studies are shown in Table 1.

RISK OF BIAS ASSESSMENT

The methodological quality of the included studies was considered low to high, according to the NOS. Six included studies achieved an average of seven stars, and two studies [29, 35] gained nine stars (Table 2).

Table 1. Main characteristics of included studies.

Study	Country	Ethnicity	Study design	Sample size	Mean age	Definition of asthma	Definition of DED	Adjustment for confounders
Alshamrani, 2017	Saudi Arabia	Arabian	Cross-sectional	Asthma: 139 Control: 1719	39.3	Questionnaire	Six-item questionnaire	Age, gender and smoking
Chia, 2003	Australia	Australian	Cross-sectional	Asthma: 135 Control: 1039	60.8	Medical history of confirmed diagnosis	Interviewer-administered questionnaire	Age and gender
Huang, 2018	Taiwan	Asian	Cohort	Asthma: 41229 Control: 164916	49.56	ICD-9-CM 493	ICD-9-CM 375.15	Age and gender
Kim, 2016	Korea	Asian	Cross-sectional	Asthma: 556 Control: 16494	50.88	Medical history	Interviewer-administered questionnaire	Age, gender, residential area, education level, occupation and history of eye surgery
Vehof, 2014	UK	Caucasian	Cross-sectional	Asthma: 608 Control: 3216	57.1	Medical history	ICD-9-CM 375.15	Age and gender
Wang, 2012	Taiwan	Asian	Cross-sectional	Asthma: 2548 Control: 45480	52.4	Elixhauser comorbidity index	ICD-9-CM 375.15	Age, gender, urbanization levels and monthly incomes

DED: dry eye diseas

Table 2. Quality assessment of included studies according to the Newcastle-Ottawa Scale.

Item/Study	Alshamrani, 2017	Chia, 2003	Huang, 2018	Kim, 2016	Vehof, 2014	Wang, 2012
Adequate definition of cases	*	*	*	*	*	*
Representativeness of cases	*	-	*	*	-	*
Selection of control subjects	-	-	*	*	-	*
Definition of control subjects	*	*	*	*	*	*
Control for important factor or additional factor	-	-	**	-	*	**
Exposure assessment	*	*	*	*	*	*
Same method of ascertainment for all subjects	*	*	*	*	*	*
Non-response rate	*	*	*	*	*	*

A study could be awarded a maximum of one star for each item except for the item "Control for important factor or additional factor".
The definition/explanation of each column of the Newcastle-Ottawa Scale is available from (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

META-ANALYSES

A random effects model was selected to analyze the effect size with modest heterogeneity among the studies (I^2 = 23%, P =0.26). The asthma group had a significantly higher prevalence of DED than the control group (OR 1.29, 95%CI 1.20–1.38; P<0.00001). In brief, there was a significant association between asthma and DED (Figure 2). Owing to the lack of data, it was not possible to detect an association between asthma and diverse subtypes of DED.

SUBGROUP ANALYSIS AND SENSITIVITY ANALYSIS

Subgroup analysis was performed according to ethnicity (Figure 3). In the stratified analysis by ethnicity, a statistically significant correlation was detected in Australians (OR 1.60, 95%CI 1.00–2.56; P=0.05), Caucasians (OR 1.54, 95%CI 1.17–2.03; P=0.002), and Asians (OR 1.29, 95%CI 1.23–1.35; P<0.00001), but this association was not significant among the Arabian population (OR: 0.96, 95%CI: 0.63–1.46; P=0.85).

SENSITIVITY ANALYSIS AND PUBLICATION BIAS

The funnel plot for the association between asthma and DED was symmetrical in vision (Figure 4). The Begg's test (z=0.38, P=0.727) and Egger's test (t=-0.40, P=0.708) also suggested no statistically significant publication bias. A sensitivity analysis confirmed the robustness of our conclusions (detailed data not shown).

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the association between asthma and DED, which examined a large dataset of six studies with a total of 278079 participants. Our current findings suggest that asthma patients have a higher risk of developing DED than non-asthmatic patients, and this significant correlation could be observed in different ethnicities, except for Arabians. In the subgroup analysis of study location, Australian, Caucasian, and Asian patients with asthma showed an increased risk of DED. It cannot be ignored that dry eye questionnaires are not only useful tools for characterizing the type and severity of dry eye, but also for evaluating the effectiveness of therapeutic interventions. Therefore, in at least 50% of the observational studies included in this meta-analysis, the diagnosis of DED was based on survey instruments (questionnaires) rather than on a clinical basis.

Some population-based studies have emphasized the possible relationship between DED and asthma. Chia et al. [30] found that after adjusting for age and sex factors, asthma is a systemic factor closely related to DED. Dogru et al. [38] found that the mean measurement of tear film breakup time was significantly lower in asthma patients than in controls, and the presence of tear film instability was higher in children with asthma, which may lead to DED in the future. In addition, in terms of treatment, some studies found that patients receiving asthma-related treatments (including leukotriene

receptor antagonists, antihistamines, and inhaled corticosteroids) have a higher risk of DED, among which antihistamines were the most frequently reported. Antihistamines are widely used to relieve allergic symptoms. However, it should not be ignored that antihistamines have a muscarinic effect on the surrounding muscarinic receptors, thereby reducing the production of tears by reducing mucin output from the goblet cells [39]. Therefore, the use of antihistamines to treat allergic diseases, including asthma, induces or exacerbates the signs and symptoms of DED.[40-42] Several studies have reported that antihistamines may be associated with DED,[43-44] and Bielory [45] found that anti-inflammatory agents used in the treatment of asthma and allergy may exacerbate dry eye complaints that commonly complicate symptoms with various forms of tear film dysfunction or conjunctival hyperreactivity.

With the emergence of many risk factors for DED, environmental conditions are associated with the occurrence and persistence of the disease. [46] One study showed that exposure to adverse environmental conditions, especially bioaerosols and air pollution, has a serious negative impact on DED symptoms.[47] This finding is largely consistent with other literature because elevated levels of air pollutants and microorganisms have been related to adverse health outcomes, including asthma and immune disorders.[48-49] Since our eyes are directly exposed to the air, the composition and characteristics of the air will undoubtedly change the anterior corneal tear film and affect the corneal nerve function.[50] Air pollution is the indicator most often associated with DED.[51-52] In addition, exposures to other pollutants have been found to be in association to symptoms and signs of DED. For example, changes in ground-level ozone concentrations are closely related to changes in DED parameters, including tear secretion and Ocular Surface Disease Index scores.[53] Both air pollutants and microbial contamination may contribute to the worsening of DED symptoms, possibly because both are associated with inflammation and oxidative stress. In animal studies, topical use of PM2.5 on mouse corneas has resulted in ocular surface damage similar to that of human dry eyes.[54-55] Humidity is also an interesting risk factor, because both low and high humidity have been shown to be related to DED.[56-57] This may be because high humidity is conducive to the growth and survival of microorganisms in the air, while low humidity leads to aqueous loss.[57]

Asthma is a consequence of complex gene-environment interactions and is an inflammatory response triggered by exposure to allergens, infection, or irritants.[23, 58] Innate and adaptive cells, including eosinophils, mast cells, lymphocytes, neutrophils, and monocytes, are activated to express or derive cytokines and chemokines and enhance inflammation and airway hyperresponsiveness, leading to airway remodeling.[59] In contrast, the most widely accepted hypothesis for the pathogenesis of DED is the immunological mechanism [60] and inflammation.[61-62] There is potential for the ocular homeostasis to be altered by innate and adaptive cells such as neutrophils, lymphocytes, eosinophils, NK cells, and macrophages, resulting in inflammatory processes that compromise both the tear film and ocular surface integrity.[63] Although the exact mechanism of DED and asthma is not completely

clear, the pathogenesis of both diseases is closely related to inflammation, which may have some shared biological pathways.

In addition, most patients with allergic diseases, such as asthma, have allergic conjunctivitis. It is estimated that as many as 20% of adults and 44% of children with asthma have symptoms of allergic conjunctivitis.[64] Allergic conjunctivitis itself can induce or aggravate dry eye by reducing the density of goblet cells and conjunctival mucin and destabilize the tear film.[65-66] In addition, DED and allergic conjunctivitis have certain similarities in signs and symptoms.[67-68] Therefore, we cannot rule out the possibility that some allergic conjunctivitis in this population may be misdiagnosed as dry eye, and the results should be interpreted cautiously.

Asthma and DED are common clinical diseases, and there is still no evidence to support a causal relationship between asthma and DED, which may have a common pathophysiological mechanism even if they occur independently. Clinicians need to diagnose the possibility of both asthma and DED. Patients with asthma should strengthen the prevention and treatment of DED and try to avoid the risk factors of DED and iatrogenic DED, including the use of contact lenses and long-term use of visual display terminals, including refractive or cataract surgery.[69-70]

LIMITATIONS

Our analysis included an in-depth and extensive literature search that included six studies, presented data of sufficient quality, and calculated outcome measures that were independent of the risk of research bias. However, our research has some limitations in the interpretation of the results. As a general defect in the meta-analysis of observational studies, we cannot rule out the possibility that certain residual factors may link asthma and DED, such as environmental factors and the use of asthma medications. Second, due to geographic and cultural differences, the lack of universal diagnostic criteria can affect the association between asthma and the incidence of DED. Finally, the results of this study do not indicate a causal relationship between asthma and DED. We recognize that this is a limitation; thus, the results should be interpreted cautiously.

CONCLUSIONS

The results of our meta-analysis show that asthma patients have a higher risk of developing DED than those without asthma, and this relationship is significant in Australians, Caucasians, and Asians. However, this association may not reflect the cause and effect if unidentified confounders account for the results. These data suggest that patients with asthma may be at risk of developing a comorbid diagnosis of DED and should try to avoid risk factors and strengthen the prevention of DED.

Author contributions Huang Qun and Zheng yanlin planned and designed the study. Xiao Xili and Wang Jing conducted rigorous literature searches and data extraction. Wang Wanjie, Liao Tingting and Wang Juan conducted the data preparation, quality assessments, and data analyses. Huang Qun and Zhang Chuantao wrote and revised the manuscript. All the authors read and approved the final manuscript.

Funding This work was supported by Sichuan Science and technology program(grant number 2020JDRC0114), "Xinglin scholar" Research Premotion Project of Chengdu University of Traditional Chinese Medicine(grant number XSGG2019016 、XGZX2003、JSZX005), "100 Talent Plan" Project of Hospital of Chengdu University of Traditional Chinese Medicine (grant number Hospital office [2020] 42), National training program for innovative backbone talents of traditional Chinese Medicine (grant number No. 91 [2019] of the State Office of Traditional Chinese Medicine), Science and technology development fund of Hospital of Chengdu University of traditional Chinese Medicine （grant number 19LW19、18MZ12）. The funder has provided only financial support for the study.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as online supplemental information. Details of the characteristics of the included studies and data extracted are available from the corresponding author at zhengyanlin@cdutcm.edu.cn.

REFERENCES

1. Bradley, J.L., et al., *Dry eye disease ranking among common reasons for seeking eye care in a large US claims database.* Clin Ophthalmol, 2019. **13**: p. 225-232.
2. Dana, R., et al., *Estimated Prevalence and Incidence of Dry Eye Disease Based on Coding Analysis of a Large, All-age United States Health Care System.* Am J Ophthalmol, 2019. **202**: p. 47-54.
3. Yasir, Z.H., et al., *Prevalence and Determinants of Dry Eye Disease among 40 Years and Older Population of Riyadh (Except Capital), Saudi Arabia.* Middle East Afr J Ophthalmol, 2019. **26**(1): p. 27-32.
4. Tan, L.L., et al., *Prevalence of and risk factors for symptomatic dry eye disease in Singapore.* Clin Exp Optom, 2015. **98**(1): p. 45-53.
5. Song, P., et al., *Variations of dry eye disease prevalence by age, sex and geographic characteristics in China: a systematic review and meta-analysis.* J Glob Health, 2018. **8**(2): p. 020503.
6. Caffery, B., et al., *Prevalence of dry eye disease in Ontario, Canada: A population-based survey.* Ocul Surf, 2019. **17**(3): p. 526-531.
7. Titiyal, J.S., et al., *Prevalence and risk factors of dry eye disease in North India: Ocular surface disease index-based cross-sectional hospital study.* Indian J Ophthalmol, 2018. **66**(2): p. 207-211.
8. Stapleton, F., et al., *TFOS DEWS II Epidemiology Report.* Ocul Surf, 2017. **15**(3): p. 334-365.
9. Rapoport, Y., et al., *A Comprehensive Review of Sex Disparities in Symptoms, Pathophysiology, and Epidemiology of Dry Eye Syndrome.* Semin Ophthalmol, 2016. **31**(4):

p. 325-36.

10. Uchino, M., *What We Know About the Epidemiology of Dry Eye Disease in Japan.* Invest Ophthalmol Vis Sci, 2018. **59**(14): p. 17-23491.
11. McDonald, M., et al., *Economic and Humanistic Burden of Dry Eye Disease in Europe, North America, and Asia: A Systematic Literature Review.* Ocul Surf, 2016. **14**(2): p. 144-67.
12. Craig, J.P., et al., *TFOS DEWS II Definition and Classification Report.* Ocul Surf, 2017. **15**(3): p. 276-283.
13. Kim, M., et al., *Dry eye disease and allergic conditions: A Korean nationwide population-*based study. Am J Rhinol Allergy, 2016. **30**(6): p. 397-401.
14. GINA Executive and Science committee. Global strategy for asthma management and prevention. 2020. https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf (accessed Feb 5, 2021).
15. To, T., et al., Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health, 2012.**12**: p. 204.
16. Ebmeier, S., et al., Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). Lancet, 2017. **390**(10098): p. 935-945.
17. Huang, K., et al., Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet, 2019. **394**(10196): p. 407-418.
18. Holt, P.G. and P.D. Sly, Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. Nat Med, 2012. **18**(5): p. 726-35.

19. Busse, W.W., R.F. Lemanske, Jr., and J.E. Gern, Role of viral respiratory infections in asthma and asthma exacerbations. Lancet, 2010. **376**(9743): p. 826-34.

20. Sbihi, H., et al., Thinking bigger: How early-life environmental exposures shape the gut microbiome and influence the development of asthma and allergic disease. Allergy, 2019. **9**(10): p. 13812.

21. 21.. Leiria, L.O., M.A. Martins, and M.J. Saad, Obesity and asthma: beyond T(H)2 inflammation. Metabolism, 2015. **64**(2): p. 172-81.

22. Hedman, L., et al., Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. Thorax, 2011. **66**(1): p. 20-5.

23. Papi, A., et al., Asthma. Lancet, 2018. 391(10122): p. 783-800.

24. Enriquez-de-Salamanca, A., S. Bonini, and M. Calonge, Molecular and cellular biomarkers in dry eye disease and ocular allergy. Curr Opin Allergy Clin Immunol, 2012. **12**(5): p. 523-33.

25. Chen, L., et al., High incidence of dry eye in young children with allergic conjunctivitis in Southwest China. Acta Ophthalmol, 2016. **94**(8): p. e727-e730.

26. Villani, E., G. Rabbiolo, and P. Nucci, Ocular allergy as a risk factor for dry eye in adults and children. Curr Opin Allergy Clin Immunol, 2018. **18**(5): p. 398-403.

27. Heck, S., et al., High probability of comorbidities in bronchial asthma in Germany. NPJ Prim Care Respir Med, 2017. **27**(1): p. 017-0026.

28. Masuda, S., et al., High prevalence and young onset of allergic rhinitis in children with bronchial asthma. Pediatr Allergy Immunol, 2008. **19**(6): p. 517-22.

29. Huang, Y.C., et al., Association between dry eye disease and asthma: a nationwide

population-based study. PeerJ, 2018. 5(6).

30. Chia, E.M., et al., Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. Clin Exp Ophthalmol, 2003. **31**(3): p. 229-32.
31. Moher, D., et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med, 2009. **6**(7): p. 21.
32. GA Wells, B.S., D O'Connell, J Peterson, V Welch, M Losos, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
33. Program, T.A. Agency for Healthcare Research and Quality. Available from: http://www.ahrq.gov/research/findings/ta/index.html.
34. Higgins, J.P., et al., Measuring inconsistency in meta-analyses. Bmj, 2003. **327**(7414): p. 557-60.
35. Wang, T.J., et al., Comorbidities of dry eye disease: a nationwide population-based study. Acta Ophthalmol, 2012. **90**(7): p. 663-8.
36. Vehof, J., et al., Prevalence and risk factors of dry eye disease in a British female cohort. Br J Ophthalmol, 2014. **98**(12): p. 1712-7.
37. Alshamrani, A.A., et al., Prevalence and Risk Factors of Dry Eye Symptoms in a Saudi Arabian Population. Middle East Afr J Ophthalmol, 2017. **24**(2): p. 67-73.
38. Dogru, M., et al., Evaluation of the tear film instability in children with allergic diseases. Cutan Ocul Toxicol, 2016. **35**(1): p. 49-52.
39. Bielory, L., Ocular toxicity of systemic asthma and allergy treatments.Curr Allergy Asthma Rep, 2006. **6**(4): p. 299-305.

40. Paulsen, A. J., et al., Dry eye in the beaver dam offspring study: Prevalence, risk factors, and health-related quality of life. Am J Ophthalmol, 2014. **157**: p.799–806.

41. Wong, J., et al., Non-hormonal systemic medications and dry eye. Ocul Surf, 2011. **9**(4): P. 212-226.

42. Ousler, G. W., et al., An evaluation of the ocular drying effects of 2 systemic antihistamines: Loratadine and cetirizine hydrochloride. Ann Allergy Asthma Immunol, 2004. **93**(5): P. 460-464.

43. Galor, A., et al., Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol, 2011. **152**(3): p.377-384.e2.

44. Paulsen, A. J., et al., 2014.Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol, 2014. **157**(4): p. 799-806.

45. Bielory, L., Ocular toxicity of systemic asthma and allergy treatments. Curr Allergy Asthma Rep, 2006. **6(**4): p. 299-305.

46. Galor, A., et al., Environmental factors affect the risk of dry eye syndrome in a United States veteran population. Ophthalmology, 2014. 121(4): P. 972-973.

47. Idarraga, M. A., et al., Relationships Between Short-Term Exposure to an Indoor Environment and Dry Eye (DE) Symptoms. J Clin Med, 2020. 9(5): P. 1316.

48. Lukcso, D., et al., Indoor environmental and air quality characteristics, building-related health symptoms, and worker productivity in a federal government building complex. Arch Environ Occup Health, 2016. 71(2): P. 85-101.

49. Fanger P. O., Indoor air quality in the 21st century: search for excellence. Indoor Air, 2000. 10(2): P. 68-73.

50. Wolkoff P., Ocular discomfort by environmental and personal risk factors altering the precorneal tear film. Toxicol Lett, 2010. 199(3): P. 203-212.

51. Mo, Z., et al., Impacts of air pollution on dry eye disease among residents in Hangzhou, China: A case-crossover study. Environ Pollut, 2019. 246: P. 183-189.

52. Novaes, P., et al., The effects of chronic exposure to traffic derived air pollution on the ocular surface. Environ Res, 2010. 110(4): P. 372-374.

53. Kim, Y., et al., Short-Term Effects of Ground-Level Ozone in Patients With Dry Eye Disease: A Prospective Clinical Study. Cornea, 2019. 38(12): P. 1483-1488.

54. Yang, Q., et al., Effects of fine particulate matter on the ocular surface: An in vitro and in vivo study. Biomed Pharmacother, 2019. 117: P. 109177.

55. Tan, G., et al., Air pollutant particulate matter 2.5 induces dry eye syndrome in mice. Sci Rep, 2018. 8(1): P. 17828.

56. Wolkoff P., Indoor air humidity, air quality, and health - An overview. Int J Hyg Environ Health, 2018. 221(3): P. 376-390.

57. Wolkoff, P., The dichotomy of relative humidity on indoor air quality. Environ Int, 2007. 33(6): P. 850-857.

58. Gibson, P.G. and V.M. McDonald, Management of severe asthma: targeting the airways, comorbidities and risk factors. Intern Med J, 2017. 47(6): p. 623-631.

59. Guida, G. and A.M. Riccio, Immune induction of airway remodeling. Semin Immunol, 2019. 14(101346): p. 101346.

60. Barabino, S., et al., Ocular surface immunity: homeostatic mechanisms and their disruption in dry eye disease. Prog Retin Eye Res, 2012. 31(3): p. 271-85.

61. Wei, Y. and P.A. Asbell, The core mechanism of dry eye disease is inflammation. Eye Contact Lens, 2014. 40(4): p. 248-56.

62. Yamaguchi, T., Inflammatory Response in Dry Eye. Invest Ophthalmol Vis Sci, 2018. 59(14): p. 17-23651.

63. Reyes, J.L., et al., Innate and Adaptive Cell Populations Driving Inflammation in Dry Eye Disease. Mediators Inflamm, 2018. 12(2532314).

64. Neto, H. J., et al., Allergic conjunctivitis in asthmatic children: as common as underreported. Ann Allergy Asthma Immunol, 2010. 105: p. 399-400.

65. Onguchi, T., et al., The impact of the onset time of atopic keratoconjunctivitis on the tear function and ocular surface findings. Am J Ophthalmol, 2006. 141: p. 569-571.

66. Hu, Y., et al., The differences of tear function and ocular surface findings in patients with atopic keratoconjunctivitis and vernal keratoconjunctivitis. Allergy, 2007. 62: p. 917-925.

67. Baudouin, C., Formes frontières de l'allergie [Conditions bordering on allergy]. J Fr Ophtalmol, 2007. 30: p.306-313.

68. Hom, M. M., et al., Allergic conjunctivitis and dry eye syndrome. Ann Allergy Asthma Immunol, 2012.108: p.163-166.

69. Uchino, M., et al., Prevalence and risk factors of dry eye disease in Japan: Koumi study. Ophthalmology, 2011. 118(12): p. 2361-7.

70. Gomes, J.A.P., et al., TFOS DEWS II iatrogenic report. Ocul Surf, 2017. 15(3): p. 511-538.

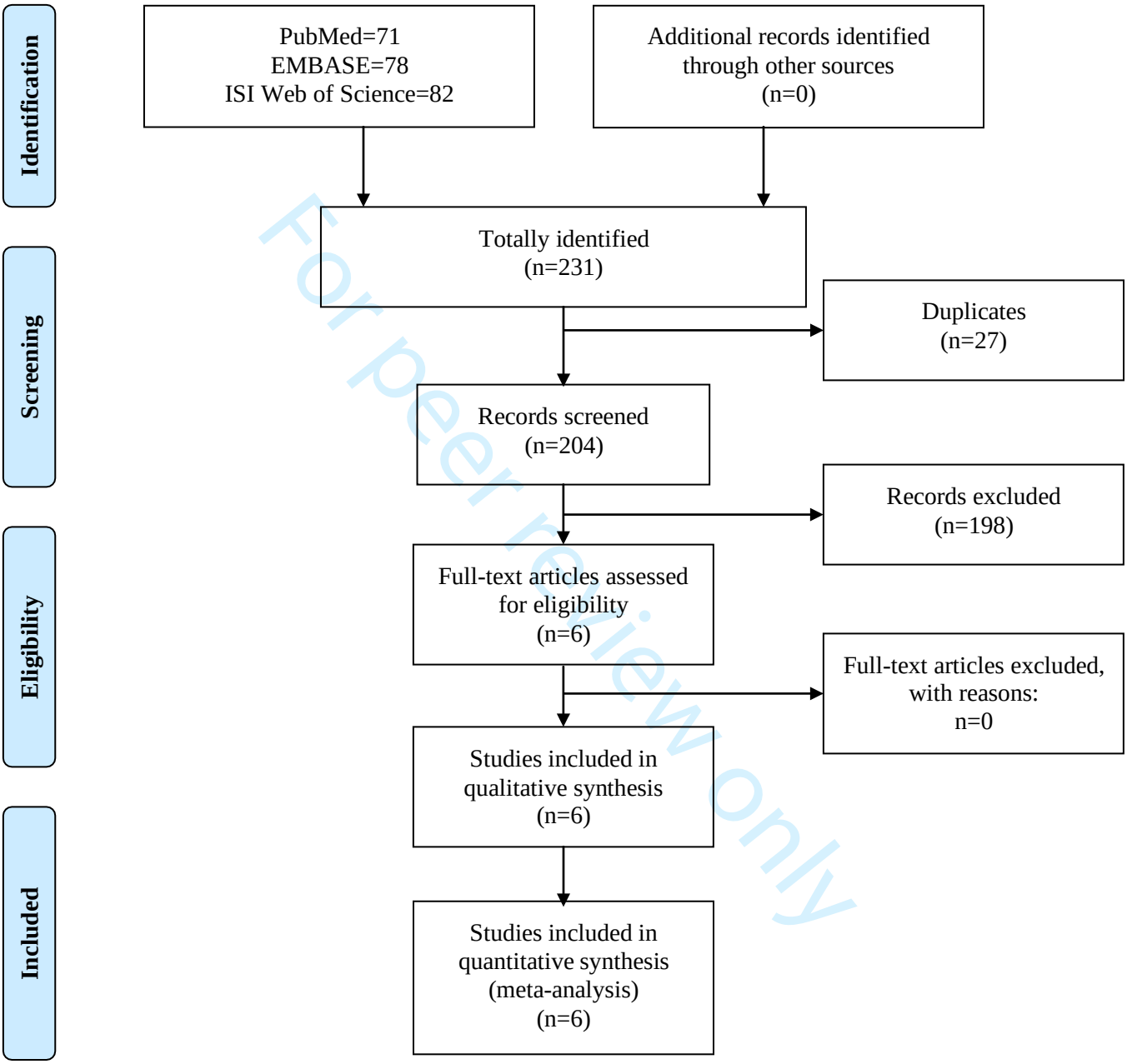
Figure Legends

Figure 1. Flow chart of literature search.

Figure 2. Meta-analysis of asthma and DED using a random-effects model.

Figure 3. Subgroup analysis by ethnicity of asthma and DED.

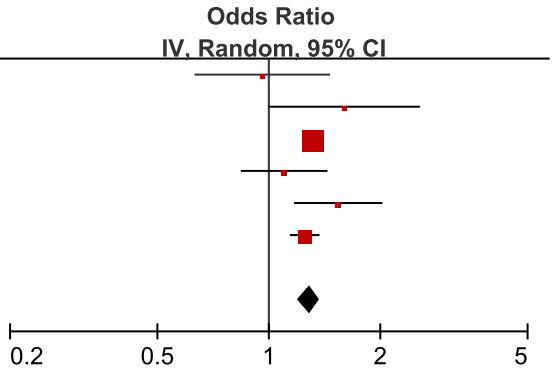
Figure 4. Funnel plot of a meta-analysis of asthma and DED.

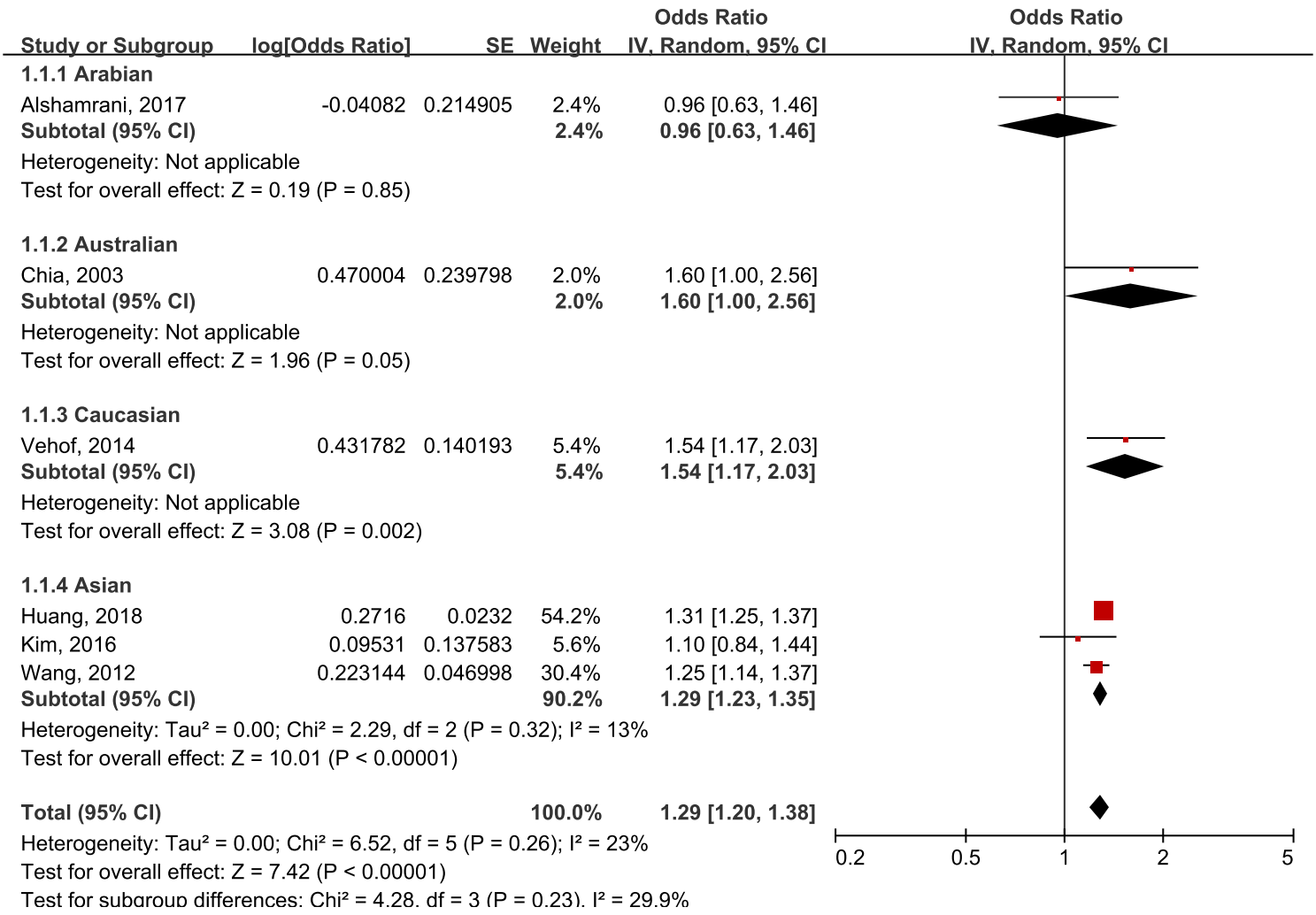


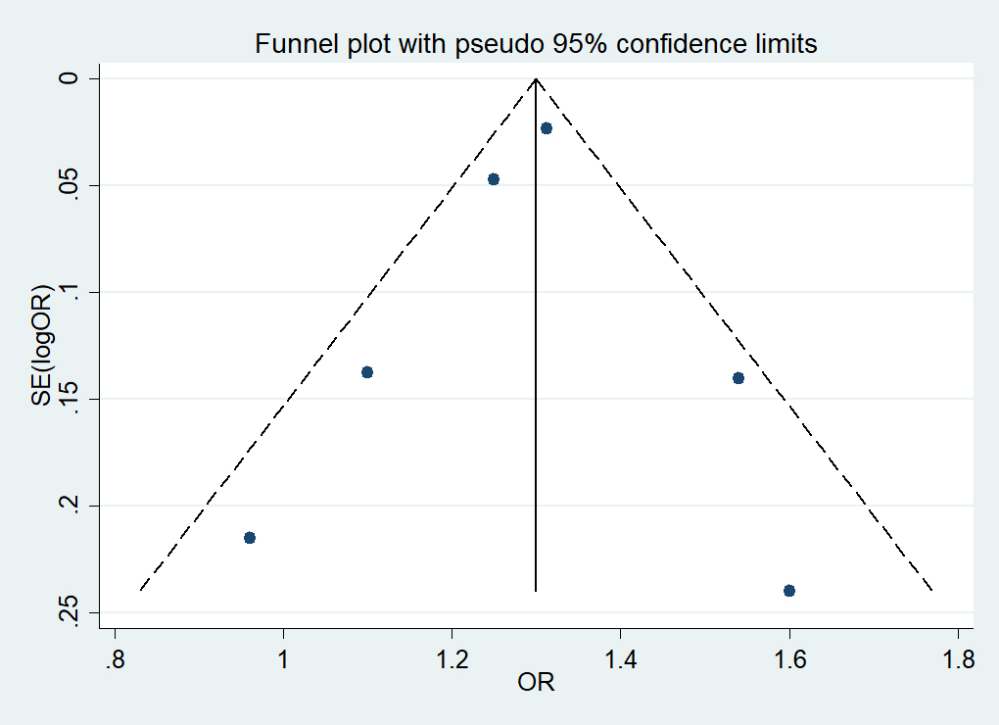
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Alshamrani, 2017	-0.04082	0.214905	2.4%	0.96 [0.63, 1.46]
Chia, 2003	0.470004	0.239798	2.0%	1.60 [1.00, 2.56]
Huang, 2018	0.2716	0.0232	54.2%	1.31 [1.25, 1.37]
Kim, 2016	0.09531	0.137583	5.6%	1.10 [0.84, 1.44]
Vehof, 2014	0.431782	0.140193	5.4%	1.54 [1.17, 2.03]
Wang, 2012	0.223144	0.046998	30.4%	1.25 [1.14, 1.37]
Total (95% CI)			**100.0%**	**1.29 [1.20, 1.38]**

Heterogeneity: Tau² = 0.00; Chi² = 6.52, df = 5 (P = 0.26); I² = 23%

Test for overall effect: Z = 7.42 (P < 0.00001)




Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Arabian
Alshamrani, 2017 -0.04082 0.214905 2.4% 0.96 [0.63, 1.46]
Subtotal (95% CI) 2.4% 0.96 [0.63, 1.46]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
1.1.2 Australian
Chia, 2003 0.470004 0.239798 2.0% 1.60 [1.00, 2.56]
Subtotal (95% CI) 2.0% 1.60 [1.00, 2.56]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)
1.1.3 Caucasian
Vehof, 2014 0.431782 0.140193 5.4% 1.54 [1.17, 2.03]
Subtotal (95% CI) 5.4% 1.54 [1.17, 2.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.08 (P = 0.002)
1.1.4 Asian
Huang, 2018 0.2716 0.0232 54.2% 1.31 [1.25, 1.37]
Kim, 2016 0.09531 0.137583 5.6% 1.10 [0.84, 1.44]
Wang, 2012 0.223144 0.046998 30.4% 1.25 [1.14, 1.37]
Subtotal (95% CI) 90.2% 1.29 [1.23, 1.35]
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 10.01 (P < 0.00001)
Total (95% CI) 100.0% 1.29 [1.20, 1.38]
Heterogeneity: Tau² = 0.00; Chi² = 6.52, df = 5 (P = 0.26); I² = 23%
Test for overall effect: Z = 7.42 (P < 0.00001)
Test for subgroup differences: Chi² = 4.28, df = 3 (P = 0.23), I² = 29.9%
0.2
0.5
1
2
5



Funnel plot of a meta-analysis of asthma and DED

360x261mm (72 x 72 DPI)

BMJ Open

Association between asthma and dry eye disease: A meta-analysis based on observational studies

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045275.R2
Article Type:	Original research
Date Submitted by the Author:	29-Sep-2021
Complete List of Authors:	huang, qun; Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Ophthalmology; Chengdu University of TCM Zheng, Yanlin; Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Ophthalmology; Chengdu University of Traditional Chinese Medicine, zhang, chuantao; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, wanjie; Chengdu University of Traditional Chinese Medicine Affiliated Hospital liao, tingting; Chengdu University of Traditional Chinese Medicine Affiliated Hospital xiao, xili; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, jing; Chengdu University of Traditional Chinese Medicine Affiliated Hospital wang, juan; Chengdu University of Traditional Chinese Medicine Affiliated Hospital
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Ophthalmology
Keywords:	Medical ophthalmology < OPHTHALMOLOGY, Asthma < THORACIC MEDICINE, Paediatric ophthalmology < OPHTHALMOLOGY, Orbital and lacrimal disorders < OPHTHALMOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association between asthma and dry eye disease: A meta-analysis based on observational studies

Running title: asthma and DED

Huang Qun[1]*, M.M., Zheng Yanlin [2†], M.M., Zhang Chuantao[3], M.D., Wang Wanjie [1], M.M., Liao Tingting[4], Xiao Xili [1], M.M., Wang Jing [1], M.M., Wang Juan[1], M.B

1 Department of Ophthalmology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

2 Clinical Medical College, Chengdu University of Traditional Chinese Medicine, Chengdu, China.

3 Department of Respiratory Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

4. Department of endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.

* first author, E-mail: skirth@163.com

† Corresponding author, E-mail: zhengyanlin@cdutcm.edu.cn

Abbreviations: DED, dry eye disease; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; MeSH, Medical Subject Headings; OR, odds ratio; NOS, Newcastle-Ottawa Scale;

ABSTRACT

Objective

This study aimed to systematically review the relationship between DED and asthma based on published population-based studies.

Data sources

PubMed, EMBASE, and ISI Web of Science from their inception were searched up to October 2019.

Study selection

Observational studies addressing the association between asthma and DED will be eligible.

Data extraction and synthesis

Two reviewers independently conducted the data extraction and quality assessment. We used a random effects model for all analyses. Subgroup analysis according to ethnicity was performed to test the influence of ethnicity on the association.

Main outcomes and measures

Six independent studies (a total of 45215 patients with asthma and 232864 control subjects) were included in this review and had an average of seven stars by the Newcastle-Ottawa Scale. Our current findings suggest that the prevalence of DED was higher in the asthma group than in the control group ($Z = 7.42$, $P<0.00001$; OR 1.29, 95% CI 1.20–1.38). In the subgroup analysis by ethnicity, Australian, Caucasian, and Asian patients with asthma showed an increased risk of DED.

OSF registration number DOI 10.17605/OSF.IO/UHN38).

Keywords

Dry eye disease; asthma; meta-analysis

Strengths and Limitations

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the association between asthma and DED.

Six included studies achieved an average of 7 stars, and two studies gained nine stars according to the NOS.

Due to geographic and cultural differences, the lack of universal diagnostic criteria can affect the association between asthma and the incidence of DED.

This significant association may not reflect a causal effect due to the cross-sectional design of the included studies.

INTRODUCTION

Dry eye disease (DED) has been the focus of attention in recent years, as it is one of the main reasons for seeking eye care in eye clinics.[1] According to surveys, the prevalence of DED is estimated to be between 5% and 50%,[2-8] the frequency of which increases with age.[9] The prevalence is driven mainly by the classification of DED, with the prevalence of signs being much higher (up to 75%) compared to symptoms.[8] The economic burden and impact of DED is considerable in terms of vision, quality of life, work productivity, and the psychological and physical impact of pain. Therefore, indirect costs account for the largest proportion of total costs because of the significant decline in work efficiency.[8, 10, 11]

DED is considered to be a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[12] Clear factors currently known to be associated with the onset of DED include age, sex, and hormones, but in recent years, it has also been found that DED is associated with asthma, allergic rhinitis, and atopic dermatitis.[13]

Asthma is one of the most common chronic immunological diseases in humans, affecting 1%–18% of the population in different countries.[14] Specifically, the prevalence of asthma varies depending on whether the disease is diagnosed by a medical doctor (4.3%), clinical/treated asthma (4.5%), or symptoms such as wheezing (8.6%), and varies by up to 21 times in different countries.[15] Its mortality rate is estimated to 0.19 deaths per 100, 000 people.[16-17] The etiology of asthma is multifactorial, including atopic sensitization,[18] viral respiratory infections,[19] environmental exposures,[20] obesity,[21] and smoking [22]. Asthma is considered to be the result of complex genetic-environmental interactions, with heterogeneity in the clinical manifestations and the type and intensity of airway inflammation and remodeling.[23]

Increasing evidence suggests that DED is associated with a high risk of ocular allergy. [24-25] Ocular allergy, particularly the severe forms of keratoconjunctivitis, has an impact on different key mechanisms of DED, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities.[26] Moreover, patients with asthma also often have allergic comorbidities such as allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy, and drug allergy.[27-28] Recently, several studies have highlighted the possible relationship between DED and asthma.[29-30] However, a possible relationship between asthma and DED remains under investigation, and well-established information is very limited. To the best of our knowledge, no meta-analysis has been performed to assess the relationship between asthma and DED. Thus, we performed the current meta-analysis to determine whether there is a link between asthma and DED using a meta-analytic approach to quantify such associations.

METHODS

This systematic review and meta-analysis conformed to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[31]

ETHICAL APPROVAL

Ethical approval, informed consent, and patient and public involvement statements were not necessary because all the data used for the analyses were extracted from available publications. The meta-analysis has been registered in the Open Science Framework (registration number: DOI 10.17605/OSF.IO/UHN38).

LITERATURE SEARCH STRATEGY

Referring to the search strategy suggested by Cochrane, two researchers independently and systematically searched three electronic databases, including PubMed, EMBASE, and ISI Web of Science, from the database inception date until October 1, 2019, without language restrictions. A combination of Medical Subject Terms (MeSHs) and free terms was used to retrieve possibly eligible publications in each electronic database, and the English search strategy was as follows: (asthma or "Asthma"[MeSH]) and (dry eye or dry eye disease or "dry eye syndrome" [MeSH]). For Chinese academic databanks, we used "gan yan" and "xiao chuan" to identify relevant Chinese articles. We also manually screened the reference lists of the original and review articles for additional eligible studies.

INCLUSION CRITERIA

The inclusion criteria were as follows: (i) the diagnosis of asthma and DED in the study group was based on well-established criteria or according to a clinical diagnosis made by clinical physicians; (ii) control subjects should be free of any history of asthma or DED, no specific restriction on sex and age was imposed; (iii) types of study were observational studies, including cross-sectional, cohort, case-control, or epidemiological studies; (iv) the main outcome was the association between DED and asthma, as indicated by odds ratio (OR) and the associated 95% confidence intervals (CI), which should be either provided directly in the original article or could be calculated based on the original data. If studies with overlapping participants were encountered, reports with the largest sample and the most recent reports were included in the present meta-analysis. If no data was available in the original article, the corresponding author of the relevant study was contacted via email. If the corresponding author did not respond after we sent three e-mails, this article was not used for quantitative synthesis. Abstracts, editorial letters, reviews, case reports, book chapters, and organizational guidelines were excluded from the analysis.

DATA EXTRACTION

According to the predetermined inclusion criteria, two reviewers (XXL and WJ) independently conducted the literature search, data extraction, and quality assessment

and were blinded to the findings of the other reviewer. After rigorous screening, the following data regarding the characteristics of the studies were extracted using a standardized collection form: first author, year of publication, country where the study was conducted, sample size, demographic characteristics of participants in different groups, strategies for confirmation of DED and asthma, and adjustment of confounding factors for effect assessment. Disagreements that occurred during the study selection were resolved through a discussion with a third reviewer (ZYL) until a consensus was reached.

QUALITY ASSESSMENT

The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in case-control and cohort studies.[32] The methodological quality of the cross-sectional studies was evaluated according to the standards of the Agency for Healthcare Research and Quality.[33] Two reviewers (WWJ and WJ) independently conducted quality assessments of the included studies and compared the results. The third reviewer (ZYL) was consulted in case of discrepancies regarding quality assessment.

DATA SYNTHESIS AND ANALYSIS

RevMan 5.3 (Copenhagen: the Nordic Cochrane Center, the Cochrane Collaboration, 2014) was used for the meta-analysis and subgroup analysis. The association between asthma and DED was estimated using adjusted OR and unadjusted OR, and the upper and lower limits of the 95%CI were extracted from each study. The confounding factors included age and sex. Before combining the data from the included studies, statistical heterogeneity among studies for each outcome was estimated using a standard Chi-square test and the Higgins I^2 test ($P>0.1$, $I^2<50\%$ indicated acceptable heterogeneity [34]). In the meta-analyses of multiple studies for a specific outcome, a random-effect estimate was calculated for pooling data across studies if statistical heterogeneity existed; however, if a low heterogeneity was detected in the meta-analysis, a random-effect estimate was also calculated, as the validity of tests of heterogeneity could be limited with a small number of component studies. In the case of high heterogeneity, subgroup analysis was carried out by ethnicity, as it was the only confounding factor consistently presented in our selected studies. Sensitivity analysis was conducted by omitting one study at a time and evaluating the resulting effect to determine the potential source of heterogeneity. Begg's rank correlation test and Egger's linear regression test using Stata version 12.0 (Stata Corp LP, USA) were used to evaluate publication bias. Statistical significance was set at $P < 0.05$ (1-sided), except for tests of heterogeneity.

PATIENT AND PUBLIC INVOLVEMENT

There was no involvement of patients or public during the outline of this project.

RESULTS

LITERATURE SEARCH

A total of 231 potential literature citations were searched initially, including 71 records from PubMed, 78 from EMBASE, and 82 from ISI Web of Science (Figure 1). Additionally, 27 duplicate articles were excluded. Based on the predetermined selection criteria, 198 studies were excluded at the title and abstract stages, and six potentially relevant studies were selected and retrieved for full-text reading and evaluation of data integrity. Finally, six studies [13, 29, 30, 35-37] met all the inclusion criteria for this systematic review and were included.

STUDY CHARACTERISTICS

Overall, the sample sizes of the included studies ranged from 1174 to 105794, of which a total of 45215 patients with asthma and 232864 control subjects were included. The included studies were published between 2003 and 2018 and involved different ethnicities, including Arabian, Australian, Asian, and Caucasian populations. The assessment of asthma and DED was inconsistent between studies, and detailed data on the main characteristics of these studies are shown in Table 1.

RISK OF BIAS ASSESSMENT

The methodological quality of the included studies was considered low to high, according to the NOS. Six included studies achieved an average of seven stars, and two studies [29, 35] gained nine stars (Table 2).

Table 1. Main characteristics of included studies.

Study	Country	Ethnicity	Study design	Sample size	Mean age	Definition of asthma	Definition of DED	Adjustment for confounders
Alshamrani, 2017	Saudi Arabia	Arabian	Cross-sectional	Asthma: 139 Control: 1719	39.3	Questionnaire	Six-item questionnaire	Age, gender and smoking
Chia, 2003	Australia	Australian	Cross-sectional	Asthma: 135 Control: 1039	60.8	Medical history of confirmed diagnosis	Interviewer-administered questionnaire	Age and gender
Huang, 2018	Taiwan	Asian	Cohort	Asthma: 41229 Control: 164916	49.56	ICD-9-CM 493	ICD-9-CM 375.15	Age and gender
Kim, 2016	Korea	Asian	Cross-sectional	Asthma: 556 Control: 16494	50.88	Medical history	Interviewer-administered questionnaire	Age, gender, residential area, education level, occupation and history of eye surgery
Vehof, 2014	UK	Caucasian	Cross-sectional	Asthma: 608 Control: 3216	57.1	Medical history	ICD-9-CM 375.15	Age and gender
Wang, 2012	Taiwan	Asian	Cross-sectional	Asthma: 2548 Control: 45480	52.4	Elixhauser comorbidity index	ICD-9-CM 375.15	Age, gender, urbanization levels and monthly incomes

DED: dry eye diseas

Table 2. Quality assessment of included studies according to the Newcastle-Ottawa Scale.

Item/Study	Alshamrani, 2017	Chia, 2003	Huang, 2018	Kim, 2016	Vehof, 2014	Wang, 2012
Adequate definition of cases	*	*	*	*	*	*
Representativeness of cases	*	-	*	*	-	*
Selection of control subjects	-	-	*	*	-	*
Definition of control subjects	*	*	*	*	*	*
Control for important factor or additional factor	-	-	**	-	*	**
Exposure assessment	*	*	*	*	*	*
Same method of ascertainment for all subjects	*	*	*	*	*	*
Non-response rate	*	*	*	*	*	*

A study could be awarded a maximum of one star for each item except for the item "Control for important factor or additional factor".
The definition/explanation of each column of the Newcastle-Ottawa Scale is available from (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

META-ANALYSES

A random effects model was selected to analyze the effect size with modest heterogeneity among the studies (I^2 = 23%, P =0.26). The asthma group had a significantly higher prevalence of DED than the control group (OR 1.29, 95%CI 1.20–1.38; P<0.00001). In brief, there was a significant association between asthma and DED (Figure 2). Owing to the lack of data, it was not possible to detect an association between asthma and diverse subtypes of DED.

SUBGROUP ANALYSIS AND SENSITIVITY ANALYSIS

Subgroup analysis was performed according to ethnicity (Figure 3). In the stratified analysis by ethnicity, a statistically significant correlation was detected in Australians (OR 1.60, 95%CI 1.00–2.56; P=0.05), Caucasians (OR 1.54, 95%CI 1.17–2.03; P=0.002), and Asians (OR 1.29, 95%CI 1.23–1.35; P<0.00001), but this association was not significant among the Arabian population (OR: 0.96, 95%CI: 0.63–1.46; P=0.85).

SENSITIVITY ANALYSIS AND PUBLICATION BIAS

The funnel plot for the association between asthma and DED was symmetrical in vision (Figure 4). The Begg's test (z=0.38, P=0.727) and Egger's test (t=-0.40, P=0.708) also suggested no statistically significant publication bias. A sensitivity analysis confirmed the robustness of our conclusions (detailed data not shown).

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the association between asthma and DED, which examined a large dataset of six studies with a total of 278079 participants. Our current findings suggest that asthma patients have a higher risk of developing DED than non-asthmatic patients, and this significant correlation could be observed in different ethnicities, except for Arabians. In the subgroup analysis of study location, Australian, Caucasian, and Asian patients with asthma showed an increased risk of DED. It cannot be ignored that dry eye questionnaires are not only useful tools for characterizing the type and severity of dry eye, but also for evaluating the effectiveness of therapeutic interventions. Therefore, in at least 50% of the observational studies included in this meta-analysis, the diagnosis of DED was based on survey instruments (questionnaires) rather than on a clinical basis.

Some population-based studies have emphasized the possible relationship between DED and asthma. Chia et al. [30] found that after adjusting for age and sex factors, asthma is a systemic factor closely related to DED. Dogru et al. [38] found that the mean measurement of tear film breakup time was significantly lower in asthma patients than in controls, and the presence of tear film instability was higher in children with asthma, which may lead to DED in the future. In addition, in terms of treatment, some studies found that patients receiving asthma-related treatments (including leukotriene

receptor antagonists, antihistamines, and inhaled corticosteroids) have a higher risk of DED, among which antihistamines were the most frequently reported. Antihistamines are widely used to relieve allergic symptoms. However, it should not be ignored that antihistamines have a muscarinic effect on the surrounding muscarinic receptors, thereby reducing the production of tears by reducing mucin output from the goblet cells [39]. Therefore, the use of antihistamines to treat allergic diseases, including asthma, induces or exacerbates the signs and symptoms of DED.[40-42] Several studies have reported that antihistamines may be associated with DED,[43-44] and Bielory [45] found that anti-inflammatory agents used in the treatment of asthma and allergy may exacerbate dry eye complaints that commonly complicate symptoms with various forms of tear film dysfunction or conjunctival hyperreactivity.

With the emergence of many risk factors for DED, environmental conditions are associated with the occurrence and persistence of the disease. [46] One study showed that exposure to adverse environmental conditions, especially bioaerosols and air pollution, has a serious negative impact on DED symptoms.[47] This finding is largely consistent with other literature because elevated levels of air pollutants and microorganisms have been related to adverse health outcomes, including asthma and immune disorders.[48-49] Since our eyes are directly exposed to the air, the composition and characteristics of the air will undoubtedly change the anterior corneal tear film and affect the corneal nerve function.[50] Air pollution is the indicator most often associated with DED.[51-52] In addition, exposures to other pollutants have been found to be in association to symptoms and signs of DED. For example, changes in ground-level ozone concentrations are closely related to changes in DED parameters, including tear secretion and Ocular Surface Disease Index scores.[53] Both air pollutants and microbial contamination may contribute to the worsening of DED symptoms, possibly because both are associated with inflammation and oxidative stress. In animal studies, topical use of PM2.5 on mouse corneas has resulted in ocular surface damage similar to that of human dry eyes.[54-55] Humidity is also an interesting risk factor, because both low and high humidity have been shown to be related to DED.[56-57] This may be because high humidity is conducive to the growth and survival of microorganisms in the air, while low humidity leads to aqueous loss.[57]

Asthma is a consequence of complex gene-environment interactions and is an inflammatory response triggered by exposure to allergens, infection, or irritants.[23, 58] Innate and adaptive cells, including eosinophils, mast cells, lymphocytes, neutrophils, and monocytes, are activated to express or derive cytokines and chemokines and enhance inflammation and airway hyperresponsiveness, leading to airway remodeling.[59] In contrast, the most widely accepted hypothesis for the pathogenesis of DED is the immunological mechanism [60] and inflammation.[61-62] There is potential for the ocular homeostasis to be altered by innate and adaptive cells such as neutrophils, lymphocytes, eosinophils, NK cells, and macrophages, resulting in inflammatory processes that compromise both the tear film and ocular surface integrity.[63] Although the exact mechanism of DED and asthma is not completely

clear, the pathogenesis of both diseases is closely related to inflammation, which may have some shared biological pathways.

In addition, most patients with allergic diseases, such as asthma, have allergic conjunctivitis. It is estimated that as many as 20% of adults and 44% of children with asthma have symptoms of allergic conjunctivitis.[64] Allergic conjunctivitis itself can induce or aggravate dry eye by reducing the density of goblet cells and conjunctival mucin and destabilize the tear film.[65-66] In addition, DED and allergic conjunctivitis have certain similarities in signs and symptoms.[67-68] Therefore, we cannot rule out the possibility that some allergic conjunctivitis in this population may be misdiagnosed as dry eye, and the results should be interpreted cautiously.

Asthma and DED are common clinical diseases, and there is still no evidence to support a causal relationship between asthma and DED, which may have a common pathophysiological mechanism even if they occur independently. Clinicians need to diagnose the possibility of both asthma and DED. Patients with asthma should strengthen the prevention and treatment of DED and try to avoid the risk factors of DED and iatrogenic DED, including the use of contact lenses and long-term use of visual display terminals, including refractive or cataract surgery.[69-70]

LIMITATIONS

Our analysis included an in-depth and extensive literature search that included six studies, presented data of sufficient quality, and calculated outcome measures that were independent of the risk of research bias. However, our research has some limitations in the interpretation of the results. As a general defect in the meta-analysis of observational studies, we cannot rule out the possibility that certain residual factors may link asthma and DED, such as environmental factors and the use of asthma medications. Second, due to geographic and cultural differences, the lack of universal diagnostic criteria can affect the association between asthma and the incidence of DED. Finally, the results of this study do not indicate a causal relationship between asthma and DED. We recognize that this is a limitation; thus, the results should be interpreted cautiously.

CONCLUSIONS

The results of our meta-analysis show that asthma patients have a higher risk of developing DED than those without asthma, and this relationship is significant in Australians, Caucasians, and Asians. However, this association may not reflect the cause and effect if unidentified confounders account for the results. These data suggest that patients with asthma may be at risk of developing a comorbid diagnosis of DED and should try to avoid risk factors and strengthen the prevention of DED.

Author contributions Huang Qun and Zheng yanlin planned and designed the study. Xiao Xili and Wang Jing conducted rigorous literature searches and data extraction. Wang Wanjie, Liao Tingting and Wang Juan conducted the data preparation, quality assessments, and data analyses. Huang Qun and Zhang Chuantao wrote and revised the manuscript. All the authors read and approved the final manuscript.

Funding This work was supported by Sichuan Science and technology program(grant number 2020JDRC0114), "Xinglin scholar" Research Premotion Project of Chengdu University of Traditional Chinese Medicine(grant number XSGG2019016 、XGZX2003、JSZX005), "100 Talent Plan" Project of Hospital of Chengdu University of Traditional Chinese Medicine (grant number Hospital office [2020] 42), National training program for innovative backbone talents of traditional Chinese Medicine (grant number No. 91 [2019] of the State Office of Traditional Chinese Medicine), Science and technology development fund of Hospital of Chengdu University of traditional Chinese Medicine （grant number 19LW19、18MZ12）. The funder has provided only financial support for the study.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as online supplemental information. Details of the characteristics of the included studies and data extracted are available from the corresponding author at zhengyanlin@cdutcm.edu.cn.

REFERENCES

1. Bradley, J.L., et al., *Dry eye disease ranking among common reasons for seeking eye care in a large US claims database.* Clin Ophthalmol, 2019. **13**: p. 225-232.
2. Dana, R., et al., *Estimated Prevalence and Incidence of Dry Eye Disease Based on Coding Analysis of a Large, All-age United States Health Care System.* Am J Ophthalmol, 2019. **202**: p. 47-54.
3. Yasir, Z.H., et al., *Prevalence and Determinants of Dry Eye Disease among 40 Years and Older Population of Riyadh (Except Capital), Saudi Arabia.* Middle East Afr J Ophthalmol, 2019. **26**(1): p. 27-32.
4. Tan, L.L., et al., *Prevalence of and risk factors for symptomatic dry eye disease in Singapore.* Clin Exp Optom, 2015. **98**(1): p. 45-53.
5. Song, P., et al., *Variations of dry eye disease prevalence by age, sex and geographic characteristics in China: a systematic review and meta-analysis.* J Glob Health, 2018. **8**(2): p. 020503.
6. Caffery, B., et al., *Prevalence of dry eye disease in Ontario, Canada: A population-based survey.* Ocul Surf, 2019. **17**(3): p. 526-531.
7. Titiyal, J.S., et al., *Prevalence and risk factors of dry eye disease in North India: Ocular surface disease index-based cross-sectional hospital study.* Indian J Ophthalmol, 2018. **66**(2): p. 207-211.
8. Stapleton, F., et al., *TFOS DEWS II Epidemiology Report.* Ocul Surf, 2017. **15**(3): p. 334-365.
9. Rapoport, Y., et al., *A Comprehensive Review of Sex Disparities in Symptoms, Pathophysiology, and Epidemiology of Dry Eye Syndrome.* Semin Ophthalmol, 2016. **31**(4):

p. 325-36.

10. Uchino, M., *What We Know About the Epidemiology of Dry Eye Disease in Japan.* Invest Ophthalmol Vis Sci, 2018. **59**(14): p. 17-23491.
11. McDonald, M., et al., *Economic and Humanistic Burden of Dry Eye Disease in Europe, North America, and Asia: A Systematic Literature Review.* Ocul Surf, 2016. **14**(2): p. 144-67.
12. Craig, J.P., et al., *TFOS DEWS II Definition and Classification Report.* Ocul Surf, 2017. **15**(3): p. 276-283.
13. Kim, M., et al., *Dry eye disease and allergic conditions: A Korean nationwide population-*based study. Am J Rhinol Allergy, 2016. **30**(6): p. 397-401.
14. GINA Executive and Science committee. Global strategy for asthma management and prevention. 2020. https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf (accessed Feb 5, 2021).
15. To, T., et al., Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health, 2012.**12**: p. 204.
16. Ebmeier, S., et al., Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). Lancet, 2017. **390**(10098): p. 935-945.
17. Huang, K., et al., Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet, 2019. **394**(10196): p. 407-418.
18. Holt, P.G. and P.D. Sly, Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. Nat Med, 2012. **18**(5): p. 726-35.

19. Busse, W.W., R.F. Lemanske, Jr., and J.E. Gern, Role of viral respiratory infections in asthma and asthma exacerbations. Lancet, 2010. **376**(9743): p. 826-34.

20. Sbihi, H., et al., Thinking bigger: How early-life environmental exposures shape the gut microbiome and influence the development of asthma and allergic disease. Allergy, 2019. **9**(10): p. 13812.

21. Leiria, L.O., M.A. Martins, and M.J. Saad, Obesity and asthma: beyond T(H)2 inflammation. Metabolism, 2015. **64**(2): p. 172-81.

22. Hedman, L., et al., Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. Thorax, 2011. **66**(1): p. 20-5.

23. Papi, A., et al., Asthma. Lancet, 2018. 391(10122): p. 783-800.

24. Enriquez-de-Salamanca, A., S. Bonini, and M. Calonge, Molecular and cellular biomarkers in dry eye disease and ocular allergy. Curr Opin Allergy Clin Immunol, 2012. **12**(5): p. 523-33.

25. Chen, L., et al., High incidence of dry eye in young children with allergic conjunctivitis in Southwest China. Acta Ophthalmol, 2016. **94**(8): p. e727-e730.

26. Villani, E., G. Rabbiolo, and P. Nucci, Ocular allergy as a risk factor for dry eye in adults and children. Curr Opin Allergy Clin Immunol, 2018. **18**(5): p. 398-403.

27. Heck, S., et al., High probability of comorbidities in bronchial asthma in Germany. NPJ Prim Care Respir Med, 2017. **27**(1): p. 017-0026.

28. Masuda, S., et al., High prevalence and young onset of allergic rhinitis in children with bronchial asthma. Pediatr Allergy Immunol, 2008. **19**(6): p. 517-22.

29. Huang, Y.C., et al., Association between dry eye disease and asthma: a nationwide

population-based study. PeerJ, 2018. 5(6).

30. Chia, E.M., et al., Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. Clin Exp Ophthalmol, 2003. **31**(3): p. 229-32.
31. Moher, D., et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med, 2009. **6**(7): p. 21.
32. GA Wells, B.S., D O'Connell, J Peterson, V Welch, M Losos, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
33. Program, T.A. Agency for Healthcare Research and Quality. Available from: http://www.ahrq.gov/research/findings/ta/index.html.
34. Higgins, J.P., et al., Measuring inconsistency in meta-analyses. Bmj, 2003. **327**(7414): p. 557-60.
35. Wang, T.J., et al., Comorbidities of dry eye disease: a nationwide population-based study. Acta Ophthalmol, 2012. **90**(7): p. 663-8.
36. Vehof, J., et al., Prevalence and risk factors of dry eye disease in a British female cohort. Br J Ophthalmol, 2014. **98**(12): p. 1712-7.
37. Alshamrani, A.A., et al., Prevalence and Risk Factors of Dry Eye Symptoms in a Saudi Arabian Population. Middle East Afr J Ophthalmol, 2017. **24**(2): p. 67-73.
38. Dogru, M., et al., Evaluation of the tear film instability in children with allergic diseases. Cutan Ocul Toxicol, 2016. **35**(1): p. 49-52.
39. Bielory, L., Ocular toxicity of systemic asthma and allergy treatments.Curr Allergy Asthma Rep, 2006. **6**(4): p. 299-305.

40. Paulsen, A. J., et al., Dry eye in the beaver dam offspring study: Prevalence, risk factors, and health-related quality of life. Am J Ophthalmol, 2014. **157**: p.799–806.

41. Wong, J., et al., Non-hormonal systemic medications and dry eye. Ocul Surf, 2011. **9**(4): P. 212-226.

42. Ousler, G. W., et al., An evaluation of the ocular drying effects of 2 systemic antihistamines: Loratadine and cetirizine hydrochloride. Ann Allergy Asthma Immunol, 2004. **93**(5): P. 460-464.

43. Galor, A., et al., Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol, 2011. **152**(3): p.377-384.e2.

44. Paulsen, A. J., et al., 2014.Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol, 2014. **157**(4): p. 799-806.

45. Bielory, L., Ocular toxicity of systemic asthma and allergy treatments. Curr Allergy Asthma Rep, 2006. **6(**4): p. 299-305.

46. Galor, A., et al., Environmental factors affect the risk of dry eye syndrome in a United States veteran population. Ophthalmology, 2014. 121(4): P. 972-973.

47. Idarraga, M. A., et al., Relationships Between Short-Term Exposure to an Indoor Environment and Dry Eye (DE) Symptoms. J Clin Med, 2020. 9(5): P. 1316.

48. Lukcso, D., et al., Indoor environmental and air quality characteristics, building-related health symptoms, and worker productivity in a federal government building complex. Arch Environ Occup Health, 2016. 71(2): P. 85-101.

49. Fanger P. O., Indoor air quality in the 21st century: search for excellence. Indoor Air, 2000. 10(2): P. 68-73.

50. Wolkoff P., Ocular discomfort by environmental and personal risk factors altering the precorneal tear film. Toxicol Lett, 2010. 199(3): P. 203-212.

51. Mo, Z., et al., Impacts of air pollution on dry eye disease among residents in Hangzhou, China: A case-crossover study. Environ Pollut, 2019. 246: P. 183-189.

52. Novaes, P., et al., The effects of chronic exposure to traffic derived air pollution on the ocular surface. Environ Res, 2010. 110(4): P. 372-374.

53. Kim, Y., et al., Short-Term Effects of Ground-Level Ozone in Patients With Dry Eye Disease: A Prospective Clinical Study. Cornea, 2019. 38(12): P. 1483-1488.

54. Yang, Q., et al., Effects of fine particulate matter on the ocular surface: An in vitro and in vivo study. Biomed Pharmacother, 2019. 117: P. 109177.

55. Tan, G., et al., Air pollutant particulate matter 2.5 induces dry eye syndrome in mice. Sci Rep, 2018. 8(1): P. 17828.

56. Wolkoff P., Indoor air humidity, air quality, and health - An overview. Int J Hyg Environ Health, 2018. 221(3): P. 376-390.

57. Wolkoff, P., The dichotomy of relative humidity on indoor air quality. Environ Int, 2007. 33(6): P. 850-857.

58. Gibson, P.G. and V.M. McDonald, Management of severe asthma: targeting the airways, comorbidities and risk factors. Intern Med J, 2017. 47(6): p. 623-631.

59. Guida, G. and A.M. Riccio, Immune induction of airway remodeling. Semin Immunol, 2019. 14(101346): p. 101346.

60. Barabino, S., et al., Ocular surface immunity: homeostatic mechanisms and their disruption in dry eye disease. Prog Retin Eye Res, 2012. 31(3): p. 271-85.

61. Wei, Y. and P.A. Asbell, The core mechanism of dry eye disease is inflammation. Eye Contact Lens, 2014. 40(4): p. 248-56.

62. Yamaguchi, T., Inflammatory Response in Dry Eye. Invest Ophthalmol Vis Sci, 2018. 59(14): p. 17-23651.

63. Reyes, J.L., et al., Innate and Adaptive Cell Populations Driving Inflammation in Dry Eye Disease. Mediators Inflamm, 2018. 12(2532314).

64. Neto, H. J., et al., Allergic conjunctivitis in asthmatic children: as common as underreported. Ann Allergy Asthma Immunol, 2010. 105: p. 399-400.

65. Onguchi, T., et al., The impact of the onset time of atopic keratoconjunctivitis on the tear function and ocular surface findings. Am J Ophthalmol, 2006. 141: p. 569-571.

66. Hu, Y., et al., The differences of tear function and ocular surface findings in patients with atopic keratoconjunctivitis and vernal keratoconjunctivitis. Allergy, 2007. 62: p. 917-925.

67. Baudouin, C., Formes frontières de l'allergie [Conditions bordering on allergy]. J Fr Ophtalmol, 2007. 30: p.306-313.

68. Hom, M. M., et al., Allergic conjunctivitis and dry eye syndrome. Ann Allergy Asthma Immunol, 2012.108: p.163-166.

69. Uchino, M., et al., Prevalence and risk factors of dry eye disease in Japan: Koumi study. Ophthalmology, 2011. 118(12): p. 2361-7.

70. Gomes, J.A.P., et al., TFOS DEWS II iatrogenic report. Ocul Surf, 2017. 15(3): p. 511-538.

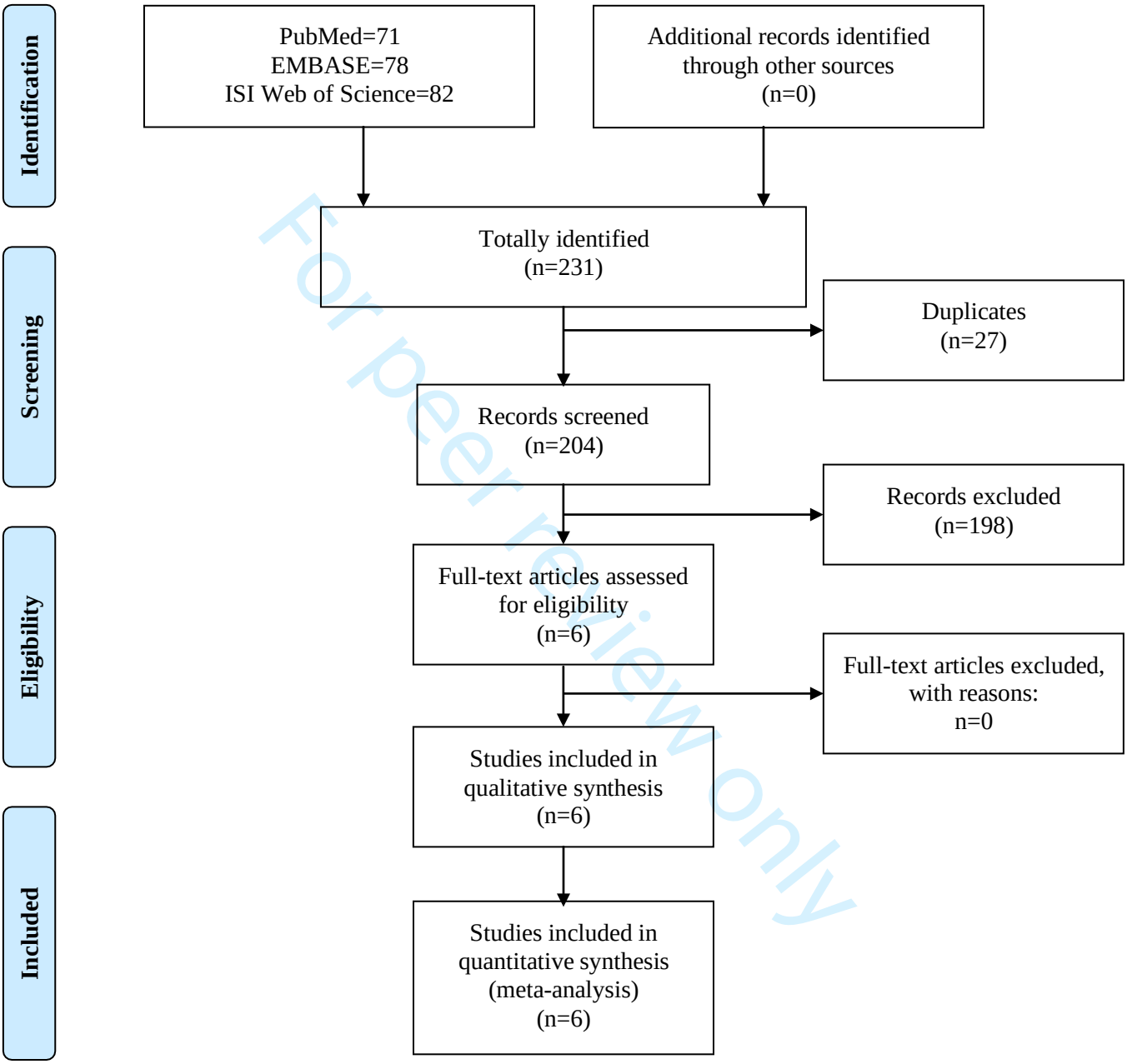
Figure Legends

Figure 1. Flow chart of literature search.

Figure 2. Meta-analysis of asthma and DED using a random-effects model.

Figure 3. Subgroup analysis by ethnicity of asthma and DED.

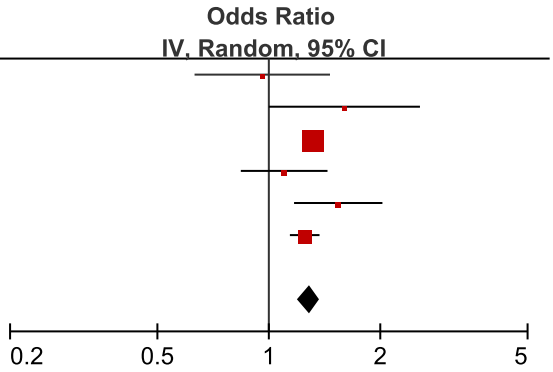
Figure 4. Funnel plot of a meta-analysis of asthma and DED.

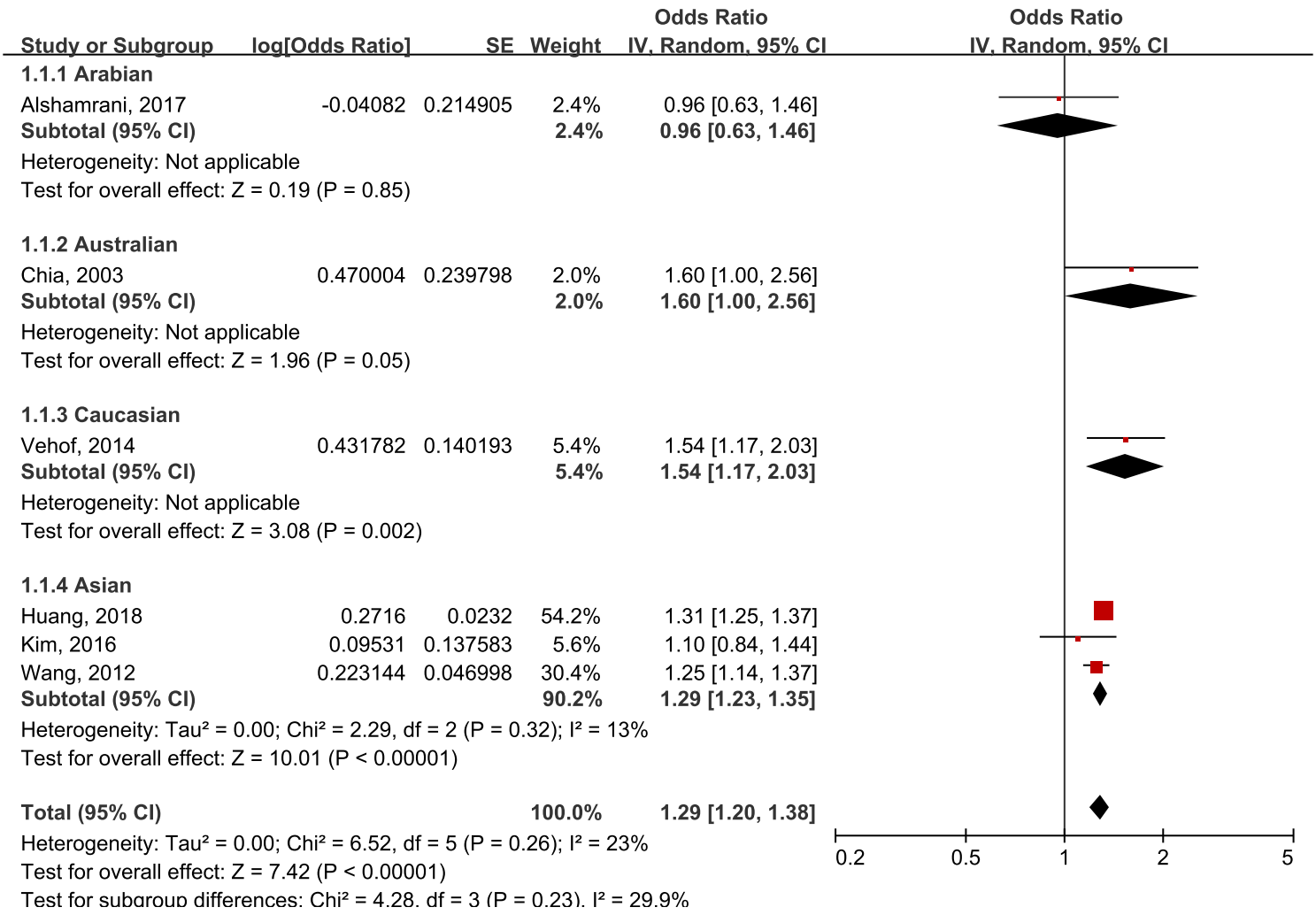


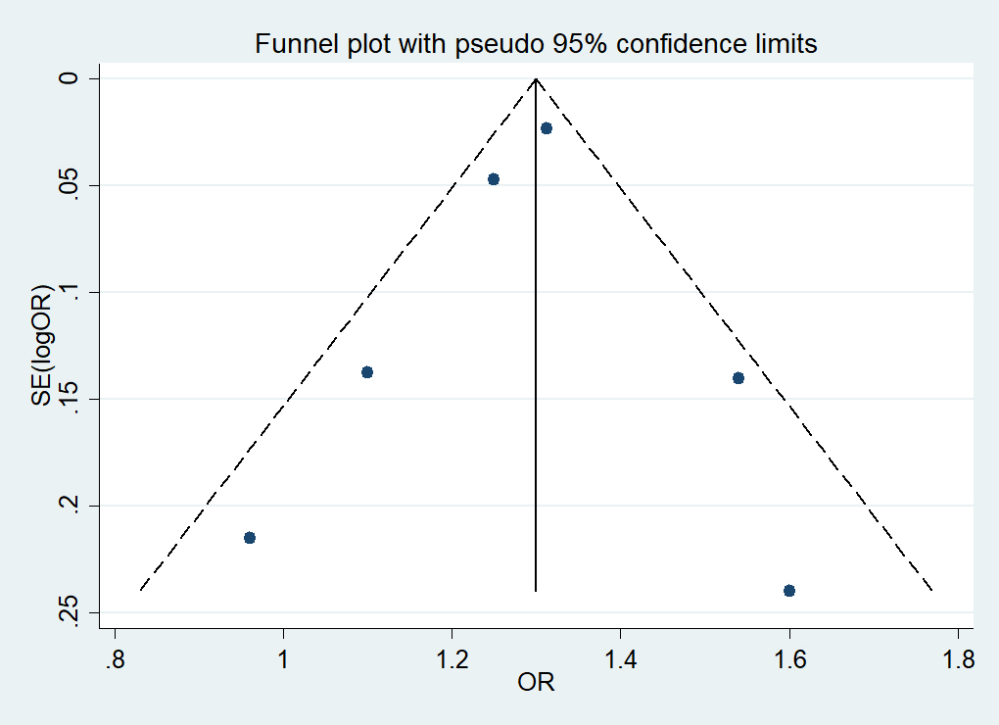
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Alshamrani, 2017	-0.04082	0.214905	2.4%	0.96 [0.63, 1.46]
Chia, 2003	0.470004	0.239798	2.0%	1.60 [1.00, 2.56]
Huang, 2018	0.2716	0.0232	54.2%	1.31 [1.25, 1.37]
Kim, 2016	0.09531	0.137583	5.6%	1.10 [0.84, 1.44]
Vehof, 2014	0.431782	0.140193	5.4%	1.54 [1.17, 2.03]
Wang, 2012	0.223144	0.046998	30.4%	1.25 [1.14, 1.37]
Total (95% CI)			**100.0%**	**1.29 [1.20, 1.38]**

Heterogeneity: Tau² = 0.00; Chi² = 6.52, df = 5 (P = 0.26); I² = 23%

Test for overall effect: Z = 7.42 (P < 0.00001)




Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Arabian
Alshamrani, 2017 -0.04082 0.214905 2.4% 0.96 [0.63, 1.46]
Subtotal (95% CI) 2.4% 0.96 [0.63, 1.46]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
1.1.2 Australian
Chia, 2003 0.470004 0.239798 2.0% 1.60 [1.00, 2.56]
Subtotal (95% CI) 2.0% 1.60 [1.00, 2.56]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)
1.1.3 Caucasian
Vehof, 2014 0.431782 0.140193 5.4% 1.54 [1.17, 2.03]
Subtotal (95% CI) 5.4% 1.54 [1.17, 2.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.08 (P = 0.002)
1.1.4 Asian
Huang, 2018 0.2716 0.0232 54.2% 1.31 [1.25, 1.37]
Kim, 2016 0.09531 0.137583 5.6% 1.10 [0.84, 1.44]
Wang, 2012 0.223144 0.046998 30.4% 1.25 [1.14, 1.37]
Subtotal (95% CI) 90.2% 1.29 [1.23, 1.35]
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 10.01 (P < 0.00001)
Total (95% CI) 100.0% 1.29 [1.20, 1.38]
Heterogeneity: Tau² = 0.00; Chi² = 6.52, df = 5 (P = 0.26); I² = 23%
Test for overall effect: Z = 7.42 (P < 0.00001)
Test for subgroup differences: Chi² = 4.28, df = 3 (P = 0.23), I² = 29.9%
0.2
0.5
1
2
5



Funnel plot of a meta-analysis of asthma and DED

360x261mm (72 x 72 DPI)